

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,

Petitioner,

v.

SURROZEN OPERATING, INC.,
Patent Owner.

Case No. PGR2026-00027

U.S. PATENT NO. 12,297,278

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF ABBREVIATIONS

Abbreviation	Term
“’278 Patent” or “Patent”	U.S. Patent No. 12,297,278 (EX1001)
“Garcia”	International Patent Publication No. WO 2016/040895 (EX1004)
“Garcia US”	U.S. Patent Publication No. 2017/0306029 (EX1011)
“Patent Owner” or “Surrozen”	Surrozen Operating, Inc.
“Petitioner” or “Merck”	Merck Sharp & Dohme LLC
“Wu”	Wu et al., <i>Simultaneous Targeting of Multiple Disease Mediators by a Dual-Variable-Domain Immunoglobulin</i> , 25 Nature Biotech. 1290 (2007) (EX1012)

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TABLE OF EXHIBITS

Exhibit No.	Description
2001	Declaration of Jeanna Wacker in Support of Motion for Admission <i>Pro Hac Vice</i>
2002	Declaration of Ashley Ross in Support of Motion for Admission <i>Pro Hac Vice</i>
2003	Chen Xue et al., <i>Wnt Signaling Pathways in Biology and Disease: Mechanisms and Therapeutic Advances</i> , 2025 NATURE 1–44 (2025)
2004	Univ. of Wis. Madison Dep’t of Biochemistry, <i>Biochemistry News</i> (2003), https://biochem.wisc.edu/wp-content/uploads/sites/1394/2023/02/2003BiochemNewsletter.pdf
2005	Anand Desai, LinkedIn, https://www.linkedin.com/in/anand-desai-b698b09/
2006	<i>Guidelines for Assessing Enablement in Utility Applications and Patents in View of the Supreme Court Decision in Amgen Inc. et al. v. Sanofi et al.</i> , 89 Fed. Reg. 1563 (2024)
2007	Sept. 12, 2022 Office Action, App. No. 16/954,484
2008	Memorandum from Coke Morgan Stewart, Acting Under Sec’y of Com. for Intell. Prop. & Acting Dir. of the U.S. Pat. & Trademark Off. to All PTAB Judges (Mar. 26, 2025), https://www.uspto.gov/sites/default/files/documents/InterimProcesses-PTABWorkloadMgmt-20250326.pdf
2009	FAQs for Interim Processes for PTAB Workload Management, USPTO, https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management (last updated Aug. 15, 2025)
2010	Declaration of Professor Karl Willert
2011	Curriculum Vitae of Professor Karl Willert

2012	Declaration of Dr. Jeffrey Ravetch
2013	Curriculum Vitae of Dr. Jeffrey Ravetch
2014	Kim, K., et al., “R-Spondin Family Members Regulate the Wnt Pathway by a Common Mechanism,” <i>Molecular Biology of the Cell</i> , 19(6), 2588-2596 (2008)
2015	Chen, B., et al., “Small molecule-mediated disruption of Wnt-dependent signaling in tissue regeneration and cancer,” <i>Nature Chemical Biology</i> , 5(2), 100-107 (2009)
2016	Lu, D., Zhao, Y., Tawatao, R., Cottam, H. B., Sen, M., Leoni, L. M., Kipps, T. J., Corr, M., & Carson, D. A. Activation of the Wnt signaling pathway in chronic lymphocytic leukemia. <i>Proceedings of the National Academy of Sciences of the United States of America</i> , 101(9), 3118–3123 (2004)
2017	Terasaki, H., Saitoh, T., Shiokawa, K., & Katoh, M. Frizzled-10, up-regulated in primary colorectal cancer, is a positive regulator of the WNT - beta-catenin - TCF signaling pathway. <i>International journal of molecular medicine</i> , 9(2), 107–112 (2002)
2018	Alrefaei, A. F., Münsterberg, A. E., & Wheeler, G. N. FZD10 regulates cell proliferation and mediates Wnt1 induced neurogenesis in the developing spinal cord. <i>PloS one</i> , 15(6), e0219721 (2020)
2019	Neuhaus, J., Weimann, A., & Berndt-Paetz, M. Immunocytochemical Analysis of Endogenous Frizzled-(Co-)Receptor Interactions and Rapid Wnt Pathway Activation in Mammalian Cells. <i>International Journal of Molecular Sciences</i> , 22(21), 12057 (2021)
2020	U.S. Patent No. 8,507,442
2021	U.S. Provisional Patent Appl. No. 62/607,877
2022	U.S. Provisional Patent Appl. No. 62/607,879

2023	Falini, B., “Generation of the first monoclonal antibody using mouse hybridomas,” <i>Haematologica</i> , 107(12), 2772-2773 (2022)
2024	Zhang, Y., “Evolution of Phage Display Libraries for Therapeutic Antibody Discovery,” <i>mAbs</i> , 15(1) (2023)
2025	Turner, K. B., et al., “Next-Generation Sequencing of a Single Domain Antibody Repertoire Reveals Quality of Phage Display Selected Candidates,” <i>PloS one</i> , 11(2), e0149393 (2016)
2026	Jakobovits, A., et al., “From XenoMouse Technology to Panitumumab, the First Fully Human Antibody Product from Transgenic Mice,” <i>Nature Biotechnology</i> , 25(10), 1134-1143 (2007)
2027	Matoba, K., et al., “Conformational Freedom of the LRP6 Ectodomain is Regulated by N-glycosylation and the Binding of the Wnt Antagonist Dkk1,” <i>Cell Reports</i> , 18(1), 32-40 (2017)
2028	DeBruine, Z. J., et al., “Assembly and Architecture of the Wnt/ β -catenin Signalosome at the Membrane,” <i>British Journal of Pharmacology</i> , 174(24), 4564-4574 (2017)
2029	U.S. Patent Appl. Publication No. 2014/0105917
2030	U.S. Patent Appl. Publication No. 2013/0230521
2031	U.S. Patent Appl. Publication No. 2008/0267955
2032	U.S. Patent Appl. Publication No. 2008/0038272
2033	U.S. Patent Appl. Publication No. 2003/0044409

****All emphasis added unless otherwise noted****

Pursuant to 37 C.F.R. § 42.107(a), Surrozen Operating, Inc. (“Patent Owner” or “Surrozen”) submits this Preliminary Response in response to the Petition for Post Grant Review (“PGR”) of U.S. Patent No. 12,297,278 (“the ’278 Patent”) filed by Merck Sharp & Dohme LLC (“Petitioner”).

I. INTRODUCTION

Each of Petitioner’s four grounds of purported unpatentability—collectively challenging all claims of the ’278 Patent—fails to meet the statutory threshold, and the Petition should be denied on the merits. 35 U.S.C. §324(a); 37 C.F.R. §42.208. Grounds 1 and 2 (written description and enablement) fail for ignoring the multitude of disclosures in the ’278 Patent’s specification, including 90 diverse examples of the claimed tetravalent molecules, complete with assay results. Petitioner’s arguments are based on a claim construction that is contrary to the claims, specification, and understanding of a POSA at the time of the invention.

Petitioner’s indefiniteness arguments (Ground 3) fare no better. They rest entirely on Petitioner’s incorrect claim construction of “Wnt surrogate molecule” as “biologically active,” and its interpretation of “fused,” contrary to the term’s plain and ordinary meaning, designed to improperly sweep in “after-arising” technology.

Finally, Petitioner’s anticipation challenge (Ground 4) rehashes the same arguments already before the Examiners, and requires Petitioner to read non-existent disclosures into Garcia (EX1004).

As further explained in the accompanying declarations of Professor Karl Willert (EX2010) and Professor Jeffrey Ravetch (EX2012), experts in Wnt signaling and antibody engineering, Petitioner's grounds are meritless. Surrozen respectfully requests that institution of the Petition be denied.

II. OVERVIEW OF THE '278 PATENT AND THE STATE OF THE ART

A. Technical Background

1. Wnt Signaling and Wnt Surrogates

The '278 Patent relates to the field of "Wnt signaling." EX1001, Title, 1:34-37. Wingless-related integration site ("Wnt") ligands and their downstream signaling pathways play key roles in the development, homeostasis, and regeneration of essential organs and tissues. *Id.*, 1:41-48.

Since the 1980s, scientists have extensively studied Wnt signaling and identified one "canonical" and two primary "noncanonical" signaling pathways. EX1001, 119:23-40; EX2003 at 9-10; EX2010 ¶¶27-28. The canonical pathway involves Frizzled ("Fzd") receptors (Fzd1-10), and "Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) or ... 6 (LRP6) as co-receptors." EX1001, 1:51-57. Canonical signaling is activated when a Wnt agonist molecule simultaneously binds a Fzd receptor and an LRP5 or LRP6 coreceptor on cell surfaces, triggering a series of downstream cellular effects that modulate gene expression. EX2003 at 2-3; EX2010 ¶27. The '278 Patent's claims focus on canonical Wnt signaling by

specifically claiming tetravalent molecules that bind to both Fzd and LRP5/6. *See* EX1001, cl. 1; EX2010 ¶33. The specification confirms this, explaining that “*the Wnt surrogate molecules of the invention* enhance the *canonical* Wnt/ β -catenin signaling pathway,”¹ EX1001, 117:33-35, as does the prosecution history, in which Applicant distinguished the prior art as “very different than the claimed molecules, which simultaneously engage two cell surface coeffector molecules (Fzds and LRP5/6) required to agonize the *canonical* Wnt signaling cascade,” EX1008 at 4006.

Prior work in the field indicated molecules consisting of a single Fzd binding region and a single LRP5/6 binding region—a 1:1 stoichiometry—could activate Wnt signaling pathways. EX1008 at 4168; *see, e.g.*, EX1004. But Surrozen’s scientists found these molecules were often ineffective. *See* EX1001, 157:52-158:47; EX1008 at 4168-70. To solve this problem, the inventors developed the molecular architecture claimed in the ’278 Patent—a *tetravalent* structure comprising two Fzd and two LRP5/6 binding regions, which they discovered reliably activates canonical Wnt signaling. EX1001, 1:51-62, 16:63-65 (“the Wnt agonists disclosed herein activate, enhance, or increase the canonical Wnt/[β]-catenin signaling pathway”), 155:11-157:15, 158:48-161:34; *see* EX2010 ¶¶72-74.

¹ Unless otherwise indicated, emphasis in quotations is Patent Owner’s own.

2. Wnt Signaling Assays

Wnt signaling activity can be “readily determined” by assaying for signaling pathway activity. EX1001, 119:54-58. Activation of the canonical pathway inhibits the destruction of the intracellular protein β -catenin, allowing it to accumulate and “translocat[e] to the nucleus where it interacts with transcription factors, e.g. TCF/LEF, to activate target genes.” *Id.*, 119:41-46; EX2010 ¶55.

The '278 Patent identifies multiple assays that detect canonical Wnt signaling, including “assays that measure: Wnt/ β -catenin target gene expression; TCF reporter gene expression; β -catenin stabilization; LRP phosphorylation; Axin translocation from cytoplasm to cell membrane and binding to LRP.” EX1001, 117:41-44. TCF (“T-cell factor”) reporter assays “assess[] changes in the transcription of TCF/LEF controlled genes to determine the level of Wnt/ β -catenin signaling activation or inhibition.” *Id.*, 117:54-58. “TOPFlash” and “Super TOPFlash” (“STF”) assays, a subset of TCF reporter assays, are and were the widely-used “go-to assay for evaluating canonical Wnt signaling.” EX2010 ¶56; EX1043 at 3 (2014 article authored by Dr. Kahn: “using the TOP-Flash reporter assay as a read-out of β -catenin-TCF activity” was the prevailing “strict definition of canonical WNT signalling”).

STF assays are highly accurate, replicable, and easy to perform, and would have been well within a POSA’s skill and knowledge in 2017. EX2010 ¶¶56-58, 62;

EX1001, 155:14-161:33 (reporting in vitro Wnt signaling data obtained with STF reporter assays).

STF assays may be performed with or without R-spondin, a biological potentiator. *See, e.g.*, EX1001, 155:29-36, 59-65, Figs. 2D, 3D. R-spondin proteins are commonly used to amplify canonical Wnt signaling activity in STF assays, but do not activate the canonical Wnt signaling pathway in the absence of a Wnt agonist. EX2010 ¶¶46, 146; EX2014 at 3; EX1001, Figs. 5A, 5E (comparing the same tetravalent Wnt surrogates in 293 STF reporter assays without and with R-spondin).

3. Historical Engineering

The inventors' work built on prior research. As Petitioner admits, "various components of the claimed molecules, *e.g.*, Fzd binding regions, Lrp5/6 binding regions, and linkers linking these regions, had been reported in the art." Pet. 55. The specification confirms that Fzd- and LRP5/6-binding antibodies and fragments thereof were "known in the art and [we]re commercially available." EX1001, 79:63-80:15, 116:25-39. The Patent also lists *hundreds* of exemplary antibodies and antigen-binding fragments (*id.*, tbls. 1A-2B), and provides POSAs with several methods known in the art to make such antibodies (*id.*, 13:37-16:16).

A POSA would be generally familiar with the different types of antigen-binding fragments and tetravalent structures falling within the scope of the claims. EX2012 ¶¶62-88.

B. Person of Ordinary Skill in the Art

Surrozen proposes that the POSA would have a Ph.D. degree in immunology, molecular biology, chemistry, or biochemistry with at least five years of experience in antibody engineering and (i) would themselves have at least two years of experience with Fzd and LRP receptors and/or Wnt signaling, or (ii) would have access to someone with such experience with Fzd and LRP receptors and/or Wnt signaling, or is on a team whose members collectively have equivalent experience. EX2012 ¶¶20-22. A POSA may also have had access to other POSAs with complementary experience in antibody engineering, Fzd and LRP receptors, and/or Wnt signaling. *Id.* Regardless of which POSA definition is used, the analysis herein would be the same.

C. Disclosures of the '278 Patent Relevant to the Claims

The '278 Patent provides a detailed and expansive disclosure of the claimed invention: tetravalent Wnt surrogates comprising “two Fzd binding regions” and “two LRP5/6 binding regions,” wherein the binding regions comprise “an antibody or antigen-binding fragment of the antibody.” EX1001, cl. 1. Each aspect of the claims is described in detail in the specification. *Infra* §IV. And each of the tetravalent molecules tested in Examples 2-18 activated canonical Wnt signaling. *Id.*, 155:14-161:33; EX2010 ¶¶72-134.

1. The '278 Patent Discloses Expansive LRP and Fzd Binding Domains

The specification discloses sequences for 91 confirmed Fzd binding clones and 211 confirmed LRP5/6 binding clones. EX1001, tbls. 1B, 2A; EX2012 ¶¶102-104; EX2010 ¶71.

Table 1A discloses complementarity-determining region (“CDR”) sequences for 448 clones initially identified as binding to one or more Fzd receptors, taking the form of different antigen-binding fragments, including VHH or sdAb. EX1001, 22:34-48, tbl. 1A. Table 1B furthers these results, reporting 91 clones confirmed to specifically bind to one or more Fzd receptors. EX1001, tbl. 1B; *see* EX2021 at 105. The scope of disclosure is broad: collectively, these Fzd binding sequences (1) bind to each of the 10 known Fzd receptors, and (2) take different antigen-binding fragment forms, including Fab, VHH, and sdAb. EX1001, 22:58-63, tbl. 1B; EX2012 ¶¶179, 211; EX2010 ¶71.

The specification also identifies commercially available prior art antibodies which can be used as “frizzled binding domains,” including “antibodies available from Biolegend” specific for human Fzd4 and Fzd9 and “antibodies available from Abcam,” specific for human Fzd4, Fzd7, Fzd8, and Fzd9,” and antibodies described in U.S. Patent Application Nos. 2014/0105917 (EX2029), 2013/0230521 (EX2030), 2008/0267955 (EX2031), 2008/0038272 (EX2032), and 2003/0044409 (EX2033) and U.S. Patent No. 8,507,442 (EX2020), each of which the ’278 Patent incorporates by reference. EX1001, 79:39-45, 79:63-80:15.

Additionally, Example 1 of U.S. Provisional Patent Application No. 62/607,877, incorporated by reference (*id.*, 22:29-34), describes a process of purifying and characterizing antibody fragments that specifically bind Fzd. EX2021 at 96-97. Sequences for candidate antibody fragments were sub-cloned into mammalian expression vectors and transfected into Expi293F cells to produce recombinant antibody fragments. EX2021 at 96. The engineered antibody fragments were fractionated and purified, and binding kinetics of the purified fragments to Fzd1-10 were determined using BLI Octet assays. *Id.*, 96-97. Example 2 of the same application selected a Fzd-binding clone (001S-A04) and evaluated the Fzd1 binding affinities of its mutants, a “large number” of which (18 of 19) “bound Fzd1 with a similar affinity as the wild type antibody fragment, demonstrating that the Fzd1 antibodies and antigen-binding fragments thereof can tolerate amino acid modifications within the CDRs.” *Id.*, 107, tbl. 2.

Table 2A of the '278 Patent also discloses 211 CDR sequences confirmed to specifically bind to LRP5/6, in the form of various antigen-binding fragments, including VHH and sdAb. EX1001, tbl. 2A, 80:50-53; EX2012 ¶104; EX2010 ¶71. Table 2A includes several prior-art LRP5/6 binding domains. EX1001, 159:10-13, 160:24-26. The specification also identifies additional prior art and commercially available antibodies that “specifically bind to LRP5 or LRP6.” *Id.*, 116:25-39.

Example 1 of U.S. Provisional Patent Application No. 62/607,879,

incorporated by reference (*id.*, 80:34-39), describes a process of purifying and characterizing antibody fragments that specifically bind LRP5/6 that mirrors the process disclosed in the '877 provisional (EX2021) for Fzd binders, with the addition of a step that measures binding affinity to LRP6e3e4. EX2022 at 93-95. Example 2 selected one LRP6-binding clone (009S-E04) and evaluated the LRP6 binding affinities of its mutants, a “large number” of which (all 11) “bound LRP6 with a similar affinity as the wild type antibody fragment, demonstrating that the LRP6 antibodies and antigen-binding fragments thereof can tolerate amino acid modifications within the CDRs.” *Id.*, 100-01, tbl. 2.

Examples 2 and 3 of the '278 Patent describe use of Octet interaction assays to confirm the binding affinity of a claimed tetravalent molecule incorporating confirmed Fzd and LRP5/6 binding domains, using two exemplary molecules (R2M3-26 and R2M3-32). EX1001, 155:18-156:14, Figs. 2C, 3C; EX2010 ¶76.

2. The '278 Patent Discloses That All Tetravalent Molecules Meeting the Claimed Binding Requirement Activate Wnt Signaling

The '278 Patent discloses tetravalent molecules that combine two Fzd binding regions and two LRP5/6 binding regions, and discloses that such tetravalent molecules can reliably activate Wnt signaling.

Table 3 lists 80 tetravalent molecules, reflecting combinations of 14 different Fzd binding regions (in total capable of binding Fzd1, Fzd2, Fzd4, Fzd5, Fzd7, Fzd8,

and Fzd9) and 18 different LRP5/6 binding regions. EX1001, tbls. 1B, 2A, 3; EX2010 ¶¶71.

Examples 2-18 then show through STF reporter assays that the claimed tetravalent molecules consistently activate Wnt signaling. EX2010 ¶¶72-134. Collectively, Examples 2-18 combine 16 different Fzd binding regions and 20 different LRP5/6 binding regions into 90 different tetravalent Wnt surrogate molecules, which collectively bind seven of the ten Fzd receptors, LRP5, and LRP6. EX2010 ¶72. These examples are highly varied, capturing differences in (1) the orientation and attachment points of the binding regions, (2) the types of antibodies and antibody fragments (incorporating IgGs, Fvs, Nabs or VHHs, Fabs, scFvs, and F(ab')₂s), and (3) the length of linkers used to bind the regions together. EX2012 ¶¶161-233; EX2010 ¶¶75-134. Every tetravalent molecule tested activated Wnt signaling. EX2010 ¶¶72-74.

Examples 5 and 6 report STF reporter activity for multiple Wnt surrogate molecules in four different cell lines. EX1001, 156:38-67, Figs. 5-6; EX2010 ¶¶87-88. The Patent also teaches a wide variety of Wnt surrogate formats, including the following thirteen tetravalent structures (EX1001, Fig. 1A):

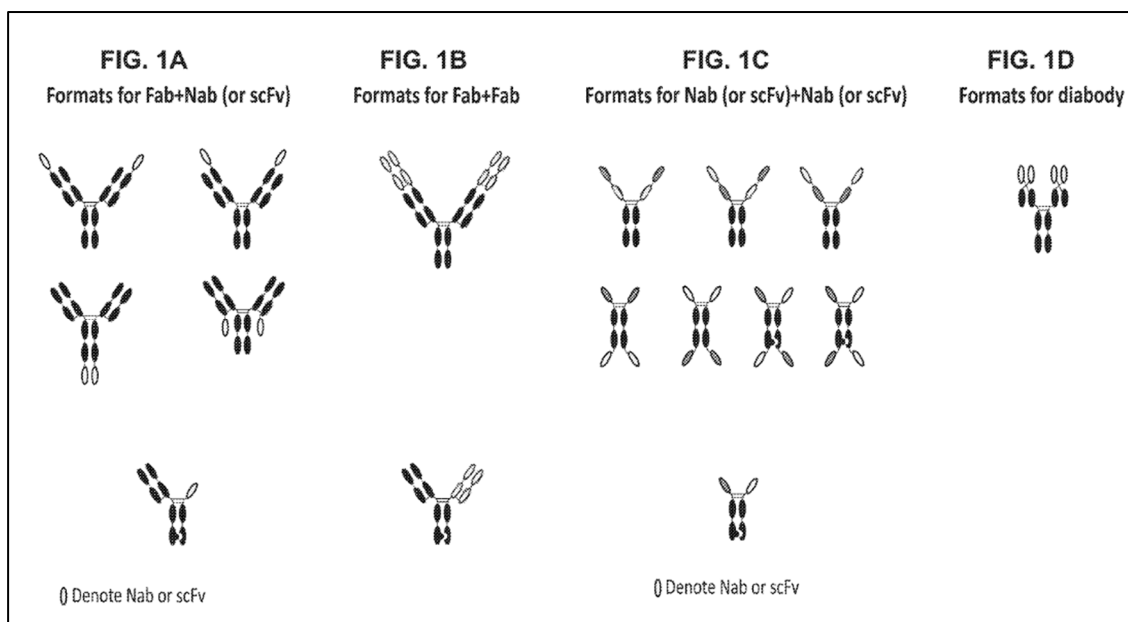


Figure 1: '278 Patent Fig. 1

III. CLAIM CONSTRUCTION

A. “Wnt Surrogate Molecule”

Claim Term	Petitioner’s Proposed Construction	Surrozen’s Proposed Construction
“Wnt surrogate molecule” (Claim 1)	Limiting; “molecule that is biologically active in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the molecule is a Wnt agonist”	Non-limiting; no construction necessary Alternatively, plain and ordinary meaning of “a molecule that binds to both (i) Fzd and (ii) LRP5 or LRP6 receptors”

“Wnt surrogate molecule” is a non-limiting preambular term that needs no construction. If Wnt surrogate molecule is construed as limiting, the term should be accorded its plain and ordinary meaning, which is “a molecule that binds to both (i) Fzd and (ii) LRP5 or LRP6 receptors.” EX2012 ¶¶127-136.

1. “Wnt Surrogate Molecule” Is Not Limiting

The preambular term “Wnt surrogate molecule” is “not limiting when the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure” of the claimed invention. *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002); *Am. Med. Sys., Inc. v. Biolitec, Inc.*, 618 F.3d 1354, 1358-59 (Fed. Cir. 2010). Here, the body of the claim defines a “structurally complete invention.”

Claim 1 recites molecules comprising two Fzd binding regions and two LRP5/6 binding regions, and it specifies how those regions are fused together “via a linker moiety.” EX1001, cl. 1. The preamble adds nothing to what is already present in the claim body and so does not provide any additional “essential structure.” *Catalina*, 289 F.3d at 808. Nor is the preambular term “Wnt surrogate molecule” “‘necessary to give life, meaning, and vitality’ to the claim.” *Catalina*, 289 F.3d at 808. It is a label that “gives a descriptive name to the set of limitations in the body of the claim that completely set forth the invention.” *Am. Med. Sys.*, 618 F.3d at 1359 (quoting *IMS Tech., Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, 1434-35 (Fed.

Cir. 2000)).

Relying on its incorrect claim construction (*see infra* §§III.A.2-3), Petitioner asserts that the preamble is a limitation that imports an agonism or biological activity requirement into the claims. Pet. 17-18. Not so. Nothing in the claims recites agonism or biological activity, and the specification and prosecution history do not support reading in such a limitation. To the extent agonism or biological activity of a “Wnt surrogate molecule” is discussed, the specification repeatedly describes that a Wnt surrogate molecule’s activity flows from its structure—expressly recited in the claim body—comprising two Fzd binding regions and two LRP5/6 binding regions. For example, the specification explains that “[c]anonical Wnt signals ... involve [LRP5 or LRP6] as co-receptors ... in addition to Fzds” and that “[a]ccordingly, there is clearly need in the art for binding moieties that specifically bind to one or more Fzd, LRP5, or LRP6 to modulate Wnt signaling pathways. ***The present invention addresses this need.***” EX1001, 1:54-62. And the specification’s examples demonstrate that while every tetravalent molecule comprising two Fzd and two LRP5/6 binding regions “activated Wnt signaling to various levels,” molecules comprising only one of each binding region were “ineffective” in doing so. *Compare, e.g., id.*, 156:38-52, *with id.*, 157:56-158:47. The specification thus confirms the “Wnt surrogate molecule” preamble is not necessary to give “life, meaning, and vitality to the claims” because the limitations recited in the body—

requiring two Fzd and two LRP5/6 binding regions—do all the necessary work.

The prosecution history does not change that conclusion. Petitioner relies on a selective quotation from the prosecution history. Pet. 18. But in the quoted Office Action Response, Applicant explained that the “claimed molecules, which simultaneously engage two cell surface coeffectors (Fzds and Lrp5/6) required to agonize the canonical wnt signaling cascade,” are different from Wu. EX1008 at 4006 (original emphasis). Applicant’s statement—that the claimed molecules have a specific structure (defined by the claim body) from which certain activity flows—does not transform the preamble into a limitation, let alone a limitation requiring agonist activity not recited in the claim.

Applicant’s use of “Wnt surrogate molecule” in the prosecution history confirms the term does not require agonist activity. In the same Office Action Response, Applicant explained that “*the Wnt surrogates* disclosed in Garcia *include one Fzd binding region and one LRP binding region*,” while further noting “the *inaccurate notion* that bivalent molecules with 1:1 Fzd/Lrp5/6 binding stoichiometry,” like Garcia’s, “were capable of agonizing a Wnt signaling pathway.” EX1008 at 4005, 4007. The inventors neither relied on “Wnt surrogate molecule” to distinguish their invention from the prior art nor gave the term an “agonist” meaning. Accordingly, the Board should reject Petitioner’s argument that “Wnt surrogate molecule” is limiting and imports an agonism or biological activity requirement into

the claims.

2. If Construed as Limiting, “Wnt Surrogate Molecule” Should be Given Its Plain and Ordinary Meaning

Even if “Wnt surrogate molecule” were found to be limiting (it should not be), it should be given its plain meaning—“a molecule that binds to both (i) Fzd and (ii) LRP5 or LRP6 receptors”—as supported by the intrinsic evidence.

The claims recite that the “Wnt surrogate molecule” comprises “Fzd binding regions” and “LRP5/6 binding regions” wherein two of each region forms a tetravalent molecule. The specification describes “Wnt surrogate molecules” as molecules that bind to both Fzd and LRP5/6. *See, e.g.*, EX1001, 16:37-39 (molecules “that bind both one or more Fzd receptors and one or both of LRP5 and/or LRP6”). And during prosecution, Applicant referred to Garcia’s prior-art molecules as “Wnt surrogate molecules” because they, too, bind Fzd and LRP5/6 (albeit, in a different format than claimed). EX1008 at 4005, 4168. Thus, the plain-and-ordinary meaning of “Wnt surrogate molecule,” supported by the intrinsic evidence, is “a molecule that binds to both (i) Fzd and (ii) LRP5 or LRP6 receptors.” EX2012 ¶125.

The plain meaning reinforces why “Wnt surrogate molecule” is not limiting in the first place, as its meaning is “merely duplicative of the limitations in the body of the claim.” *Am. Med. Sys.*, 618 F.3d at 1359.

3. Petitioner’s Proposed Construction Is Incorrect

Petitioner construes “Wnt surrogate molecule” based on purported

lexicography (there is none) and then argues that construction renders the claims indefinite. *Compare* Pet. 17, *with* 75. This fails, as discussed below for indefiniteness. *Infra* §VI.A. Petitioner’s construction is also incorrect.

Foremost, the law does not read in functional requirements where, as here, the claims are structural. *See supra* §III.A.1-2. Where “a claim uses clear structural language, it is generally improper to interpret it as having functional requirements,” especially when “nothing in the claim language itself [] requires [the claimed molecules] to perform [a] function.” *Schwing GmbH v. Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1324 (Fed. Cir. 2002); *see Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (improper to “import[] limitations from the specification into the claims”).

Petitioner tries to import functional language into the claims by arguing lexicography, but its arguments fail. Lexicography requires that the inventors “clearly express [the] intent” to “redefin[e] the meaning of particular claim terms away from their ordinary meaning.” *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1370 (Fed. Cir. 2005). The inventors here did not define “Wnt surrogate molecule” in the specification. The purported definition on which Petitioner relies (EX1001, 16:52-56) stands in contrast to other places in the specification where the inventors used definitional language like “[t]he term [____] as used herein.” *See, e.g.*, EX1001, 11:52-12:23, 13:14-36, 16:56-17:2. If anything,

the specification uses permissive language when describing Wnt surrogate molecules (*id.*, 117:26 (“Wnt surrogate molecules **may** activate Wnt signaling”)), foreclosing any “clearly express[ed] ... intent” to redefine “Wnt surrogate molecule” to mean a “biologically active” “Wnt agonist.” *Merck*, 395 F.3d at 1370.

That the Patent uses “Wnt surrogate” to refer to both Wnt agonists and “ineffective” molecules devoid of the threshold “biological activity” Merck stresses distinguishes this case from *Honeywell*, where the “fuel filter” identified as the “present invention” was the only claimed “fuel component” disclosed or suggested. *Honeywell Int’l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1318 (Fed. Cir. 2006). *Trading Technologies* is also inapposite: in that specification, a manual re-centering command identified as a feature of the “present invention” was consistent with how the claimed “re-centering command” was discussed throughout the entire specification. *Trading Techs., Int’l, Inc. v. e-Speed, Inc.*, 595 F.3d 1340, 1353 (Fed. Cir. 2010). Unlike the specification in *Trading Technologies*, which “contain[ed] no reference to automatic recentering,” *id.*, the Patent contains numerous references to “Wnt surrogate[s]” that were “ineffective” at activating Wnt signaling and thus without the “biological activity” Merck seeks to import into the claim. *Compare* EX1001, tbl. 3 (“Wnt Surrogate Sequences,” listing bivalent molecules R2M3-26Fab, R2M3-32Fab, and R2M3-26Hetero-Ig), *with id.* 157:55-158:47 (describing bivalent molecules as “ineffective”); EX2012 ¶133.

B. “Wherein Each of the Two LRP5/6 Binding Regions Is Fused to One of the Two Fzd Binding Regions via a Linker Moiety”

Claim Term	Merck’s Proposed Construction	Surrozen’s Proposed Construction
“wherein each of the two LRP5/6 binding regions is fused to one of the two Fzd binding regions via a linker moiety” (claim 1)	“wherein each of the two LRP5/6 binding regions is connected directly via a linker moiety to one and only one Fzd binding region”	Plain and ordinary meaning of “wherein each of the two LRP5/6 binding regions is bound to at least one of the two Fzd binding regions via a linker moiety”

Because Petitioner has not established that construction of this term is “necessary to resolve the controversy,” it should not be construed. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). To the extent claim construction is required, the term should have its plain-and-ordinary meaning, which is “wherein each of the two LRP5/6 binding regions is bound to at least one of the two Fzd binding regions via a linker moiety.”

Petitioner first attempts to import a requirement that the two binding regions are “connected directly,” Pet. 19, which has no grounding in the specification,

excludes numerous embodiments, and is contradicted by Petitioner’s own analysis. Surrozen’s construction, by contrast, is consistent with the specification’s use, and a POSA’s understanding, of “fused” in the context of the invention.

The specification uses “fused” interchangeably with “bound.” *See, e.g.*, EX1001, 17:46-48 (“polypeptides, e.g., linked or bound to each other or fused to each other”), 22:23-27 (“a Fzd binding region ... fused or bound to a polypeptide that specifically binds to one or more Fzd receptor”), 18:29-31; EX2012 ¶139. This is consistent with the tetravalent structures disclosed as embodiments of the invention. Figure 1C depicts multiple claimed molecules where the Fzd and LRP5/6 binding regions are not “connected directly” to one another (as Petitioner’s construction requires) but are instead bound via linker through intervening Fc regions and disulfide bonds. EX1001, Fig. 1C; EX2012 ¶139.

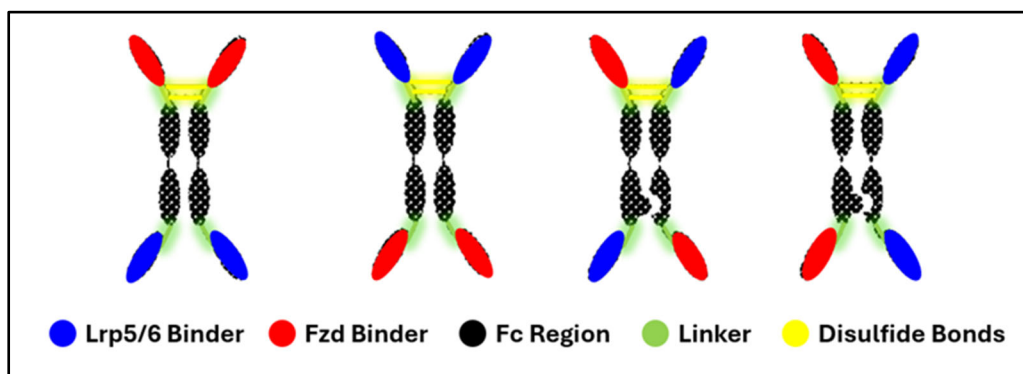


Figure 2: '278 Patent Figure 1C (annotated)

Numerous claimed embodiments with these structures—incorporating an intervening Fc region between the Fzd and LRP5/6 binding regions—were made and tested in Examples 13 and 14. EX1001, 158:54-159:39, Figs. 13, 14; EX2012 ¶143.

And Surrozen’s construction is consistent with a POSA’s understanding of the term. It is commonplace to refer to an antigen-binding fragment as being “fused” to an IgG or Fc region to indicate they are bound to each other. EX2012 ¶138.

Petitioner agrees that “fused” means “connected” (*i.e.*, bound), but adds the extraneous, unclear term “*directly*.” Pet. 19. The Federal Circuit has “repeatedly rejected” attempts to “add[] language without support from the specification or prosecution history, altering otherwise unambiguous claim language.” *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1299 (Fed. Cir. 2014). Just so here. Petitioner cites nothing in the specification that indicates “fused” requires “direct” linkage.

Rather, the specification makes clear that “fused” does not require “direct” connection. It repeatedly distinguishes antigen-binding fragments that are “fused directly” (not claimed) from those that are “fused via a linker moiety” (claimed). EX1001, 20:28-31; *id.*, 17:52-54, 18:36-40, 19:50-54, 21:30-33; EX2012 ¶140. If “fused” required “connected directly,” identification of elements in the specification that are “fused directly” would be redundant.

Petitioner also cites the specification’s use of the word “unfused” to argue direct connection is required (Pet. 20-21) but ignores the context in which “unfused” was used. When focusing on two adjacent components, it is natural to describe them as “unbound” or “unfused” when they are not joined at the location of adjacency,

even if indirectly bound. *See* EX1001, 20:55-60, 150:59-151:3; EX2012 ¶149. This does not alter the meaning of “bound” to exclude elements indirectly bound. So too with “fused” and “unfused.” *Id.*

Petitioner’s proposed construction of fused “to refer to direct connections, distinct from indirect connections among and within polypeptide chains (e.g., through disulfide bonds)” (Pet. 19; EX1002 ¶110) is also contradicted by its own analysis and by its declarant. EX2012 ¶¶140-141. Dr. McDonnell recognizes that the claimed molecules encompass formats where the binding regions are separated by a linker *and* an intervening Fc domain that is “‘necessary’ to hold different polypeptide chains together.” EX1002 ¶124, Fig. 9. All twenty-one topologies Petitioner uses to estimate the claims’ scope include an intervening Fc region between binding regions. *Id.*; EX2012 ¶140. But as Dr. Ravetch explains, connection via an Fc region, like connection via disulfide bonds, is an “indirect connection[] among and within polypeptide chains.” Pet. 19; EX2012 ¶142. Molecules with such indirect binding are clearly within the claim’s scope. Petitioner’s declarant also appears to entirely disagree with Petitioner’s understanding of “direct” connection: Dr. McDonnell describes the molecules in Tao as a structure in which “each of the two Lrp5/6 binding regions is *directly linked* via a linker moiety to both Fzd binding regions,” EX1002 ¶201, even though the diabodies in Tao’s molecules are indirectly bound via an Fc region and at least two linkers, EX2012 ¶141:

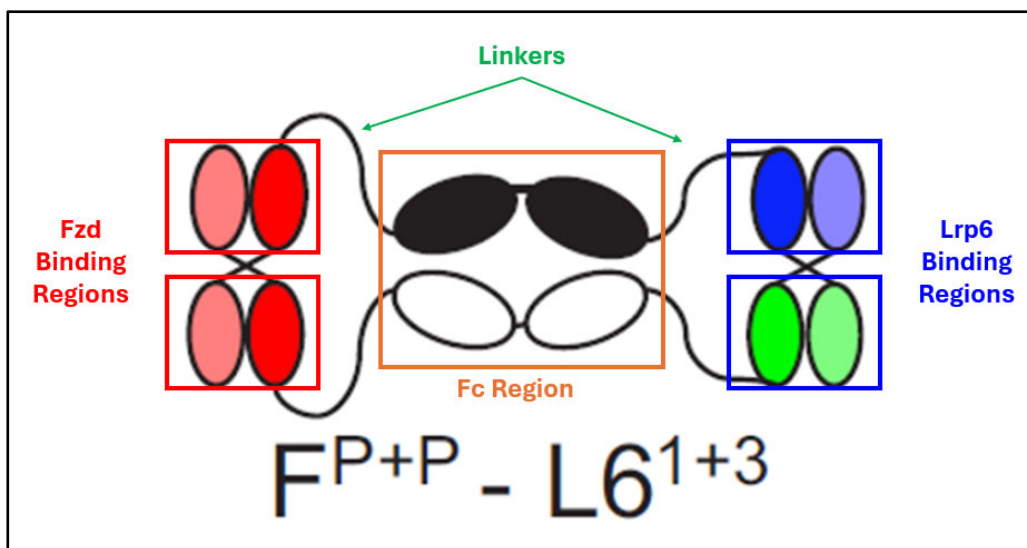


Figure 3: Tao (EX1072) at Fig. 1C (annotated)

Petitioner’s construction also improperly excludes at least seven embodiments tested in Examples 13 and 14. EX2012 ¶143; EX1001, 158:54-159:39, Figs. 1C, 13D-13F, 14E-14G. “[T]here is a strong presumption against a claim construction that excludes a disclosed embodiment.” *Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1381 (Fed. Cir. 2018). Were Petitioner’s construction adopted, binding regions separated by an intervening Fc region would be considered to have “indirect connection” such that the Fzd and LRP5/6 binding regions are not “fused.” EX2012 ¶143. Yet the Patent describes these molecules as embodiments of the claims. EX1001, 21:20-24, 172:36-37 (describing the preceding examples as “various embodiments”). Petitioner’s construction should be rejected.

Continuing, Petitioner argues that the phrase “one of the two Fzd binding regions” means “one and only one Fzd binding region.” Pet. 21. That is incorrect.

The plain-and-ordinary meaning of “one of the two” in view of the specification is “at least one of the two.” The specification discloses numerous tetravalent structures and embodiments, and in every embodiment, the LRP5/6 binding regions are “fused via a linker moiety,” *i.e.*, bound via a linker moiety (and other intervening elements), to **both** Fzd binding regions. *See, e.g.*, EX1001, Fig. 1; EX2012 ¶157. To construe “one of the two” to mean anything other than “at least one of the two” would be to exclude every disclosed embodiment from the scope of the claims. Petitioner cannot overcome the “strong presumption” required for such exclusion. *Nobel Biocare*, 903 F.3d at 1381.

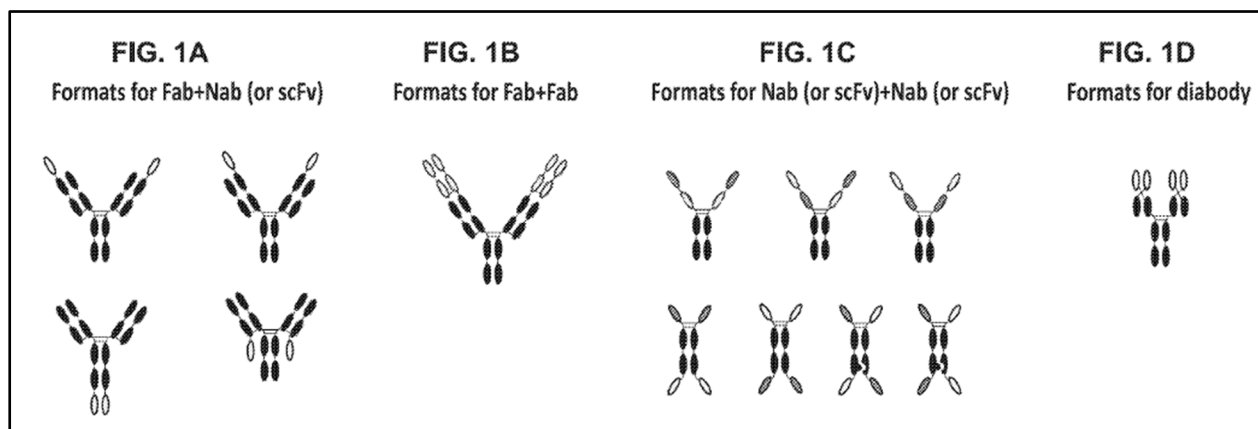


Figure 4: '278 Patent Figure 1

Petitioner’s citation to *WMS Gaming, Inc. v. Int’l Game Tech.*, 184 F.3d 1339 (Fed. Cir. 1999) is inapposite. Plain and ordinary meaning is determined by reference to the specification, *Phillips*, 415 F.3d at 1314, and **this** specification makes clear that “one of the two” means “at least one of the two.” Petitioner’s proposed construction finds no support in this specification or claim language. *See*

Pet. 22-23. Indeed, if the inventors wished to restrict the number of Fzd-LRP5/6 connections (thereby excluding embodiments from the claims), they would have used the language “*only one*” or “*one and only one*,” as they did elsewhere. *See, e.g.,* EX1001, 3:55-57 (describing inclusion of “only one” of two binding regions within a full IgG).

Petitioner’s declarant attempts to justify his proposed constructions on the ground that the claims would otherwise cover formats “unknown to a POSA as of 2017:” specifically, formats where the “binding regions comprised antibody fragments known as ‘diabody.’” EX1002 ¶¶200-201. This fails. The ’278 Patent describes formats where the binding regions are diabodies. EX1001, 21:39-51, 151:23-28, Fig. 1D; EX2012 ¶¶69, 177, 278.

IV. CLAIMS 1-5 ARE NOT INVALID FOR LACK OF WRITTEN DESCRIPTION

A. Claim 1 Is Not Invalid for Lack of Written Description Under Patent Owner’s Claim Construction

Claim 1 encompasses a limited set of novel tetravalent molecules that are described in the specification. As discussed above, “Wnt surrogate molecule” in the preamble is non-limiting and requires no construction. *Supra* §III.A.1. Under this interpretation, claim 1 is directed to molecules with binding regions having a 2:2 Fzd:LRP5/6 stoichiometry. Contrary to Petitioner’s argument, claim 1 does not require the claimed molecules to have a particular functionality, such as assay

activity or therapeutic effect. The law does not read in such a functional requirement where, as here, the claims are structural. *Supra* §III.A.3.

Given the numerous exemplary embodiments and detailed instructions in the '278 Patent from which a POSA could visualize and recognize members of the claimed genus, there can be no doubt that the inventors possessed the full scope of their claims. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010). Here, the inventors discovered unexpectedly that “efficient WNT surrogate signaling might require the clustering of receptor complexes of more than one FZD and one LRP,” and that **tetravalent** molecules—with a 2:2 Fzd:LRP5/6 stoichiometry—could reliably activate Wnt signaling. EX1008 at 4170-71; *see* EX2010 ¶¶72-74. Their invention is not the genus of Fzd and LRP5/6 binding regions, which were already “known in the art and ... commercially available,” EX1001, 79:63-80:15, 116:25-39, but rather a structure that combines these well-known binding regions in a new way, *i.e.*, in the claimed tetravalent format, which the inventors discovered confers “greatly superior activity” compared “to those having 1:1 Fzd binder:Lrp5/6 binder stoichiometry” and allows for reliable Wnt signaling. EX1008 at 4170; EX2012 ¶¶224, 234-254.

As discussed below, the inventors not only disclosed how to make and use the claimed tetravalent molecules, but disclosed 90 diverse, representative species falling within the scope of the claims. EX2012 ¶¶161-233; EX2010 ¶72. This case

is consistent with Federal Circuit precedent that has held, in the case of a “well-known genus used as part of a different invention,” the specification, “read in light of the background knowledge in the art,” can provide a representative number of species. *Teva Pharms. Int’l v. Eli Lilly & Co.*, 172 F.4th 1367, 1374-77 (Fed. Cir. 2026) (reversing JMOL of invalidity for lack of written description); *see Ariad*, 598 F.3d at 1351 (“the test for sufficiency is whether the disclosure ... reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date”); *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (the specification need not re-describe known elements and “add unnecessary bulk to the specification”); *infra* §IV.A.3. “A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language.” *Falko-Gunter*, 448 F.3d at 1366 (quoting *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005)). The claims are not invalid for inadequate written description.

1. The Specification Extensively Describes the Claimed Fzd and LRP5/6 Binding Regions

The ’278 Patent specification provides extensive examples and methods of identification for the binding regions in claim 1:

- 91 confirmed Fzd binding regions and 211 confirmed LRP5/6 binding regions that comprise an antibody or antigen-binding fragment of the antibody (EX1001, tbls. 1B, 2A);
- binding regions for all 10 Fzd receptors and LRP5 and LRP6 coreceptors that comprise an antibody or antigen-binding fragment of the antibody (*id.*, tbls. 1B, 2A);
- both “frizzled specific antibodies” and “[a]ntibodies that specifically bind to LRP5 or LRP6 are known in the art and are commercially available” (*id.*, 79:63-80:15, 116:25-39; *supra* §§II.A.3, II.C.1);
- “methods to determine [] specific or preferential binding” of a Fzd and LRP5/6 binding region are “well known in the art” (*id.*, 120:61-121:9; *see supra* §II.C.1);
- “methods for obtaining an antibody or antigen binding domain specific for a Fzd receptor” by modifying and testing a VH domain (*id.*, 120:25-36).

Based on these disclosures, a POSA in 2017 would have understood that the inventors were in possession of the claimed genus of Fzd and LRP5/6 binding regions. *See* EX2012 ¶¶224-232. This extensive disclosure is fundamentally unlike the “research plan” in *University of Rochester v. G.D. Searle & Co.*, where the patent did “not disclose *any* compounds that can be used in its claimed methods,” only “a

hoped-for function for an as-yet-to-be-discovered compound.” 358 F.3d 916, 927-28 (Fed. Cir. 2004).

Moreover, where, as here, the claims recite a novel combination of known elements, the patent specification need not re-describe the known elements and “add unnecessary bulk to the specification.” *Falko-Gunter*, 448 F.3d at 1368; *see Ariad Pharms*, 598 F.3d at 1351; *Teva*, 172 F.4th at 1376 (reversing JMOL of invalidity for lack of written description; the specification’s disclosure of what is “well known” and “routine” in the art can support written description).

Falko-Gunter is instructive. The patent claimed Inglis’s novel poxvirus vaccines made from known DNA elements. *Falko-Gunter*, 448 F.3d at 1360-61. Falkner argued Inglis’s priority applications did not describe “‘essential regions’ of any poxvirus[es]” sufficient to provide written description. *Id.* at 1361-62, 1367. The court rejected that argument because “recit[ing] known DNA structures ... would serve no goal of the written description requirement.” *Id.* at 1368. Thus, the court held that recitation of known structure is not required. *Id.* at 1367-68. Where POSAs would understand from the specification what DNA elements to use and would know their structure from the art, the specification did not need to redescribe those elements. *Id.*

So too here. The specification confirms Fzd and LRP5/6 binding regions were “known in the art and are commercially available” at the time of the invention

(EX1001, 79:63-80:15, 116:25-39), a fact Petitioner does not dispute (Pet. 55). To satisfy the written description requirement, the '278 Patent need not describe these well-known and commercially-available binding regions. The specification nonetheless provides hundreds of exemplary Fzd and LRP5/6 binding regions that POSAs would have used when making the claimed tetravalent molecules. *Supra* §II.C.1. Petitioner criticizes this disclosure as not representative because a subset of the disclosed binding regions were used in the tetravalent molecules (Pet. 45-46), but a “specification do[es] not [have to] contain examples explicitly covering the full scope of the claim language,” *Falko-Gunter*, 448 F.3d at 1366 (quoting *LizardTech*, 424 F.3d at 1345). Taken together, these disclosures more than satisfy the written-description requirement.

2. The Claimed Antibodies and Antigen-Binding Fragments Are Described in the Specification and Well-Known in the Art

The specification also describes the claimed antibodies and antigen-binding fragments, spanning IgGs (Examples 2, 3, 8, 9, 15, 17), Fvs (Example 18), scFvs (Example 14), Fabs (Example 15), Nabs or VHHs (Examples 5-9, 13, 17), F(ab')₂s (Example 16), and diabodies (EX1001, 11:39-40, 13:55-64, 14:20-54, 21:39-51, 151:23-28, Fig. 1D), across multiple formats (Fig. 1). EX2012 ¶177. Each of the identified antigen-binding fragments were well-known in the art, and a POSA would have experience assembling these fragments into tetravalent molecules. EX2012

¶¶62-71; EX1001, 13:14-16:16. Based on the specification, a POSA would have understood the inventors to possess the range of possible antibodies and antigen-binding fragments. EX2012 ¶¶175-181.

3. The Claimed Fzd and LRP5/6 Binding Regions in a Tetravalent Format Are Described in the Specification

Based on the '278 Patent specification's descriptions of Fzd and LRP5/6 binders and antibodies and antigen-binding fragments, and the extensive experiments disclosed in the examples, a POSA would understand that the inventors were in possession of the claimed tetravalent molecules. As the inventors explained, they discovered unexpected benefits for molecules that bind Fzd and LRP5/6 receptors when they are arranged in a *tetravalent* format with 2:2 Fzd:LRP5/6 stoichiometry. For example, 2:2 tetravalent molecules may help with more efficient Wnt surrogate signaling by clustering receptor complexes of Fzd and LRP. EX1008 at 4170-71. Though many Fzd and LRP5/6 binding regions were already "known in the art and [were] commercially available" (EX1001, 79:63-80:15, 116:25-39) in 2017, it was the inventors' discovery of the tetravalent molecules (2:2 Fzd:LRP5/6 stoichiometry), that resulted in "greatly superior activity" compared "to those having 1:1 ... stoichiometry." EX1008 at 4170; *see* EX2010 ¶¶106-110, 121.

A POSA would understand that the inventors possessed the claimed molecules from the examples and because the specification describes the Fzd and LRP5/6 binding regions (including those disclosed in the specification and also those

described as known in the art). *See* EX1001, 2:65-4:37, 18:26-22:22, Fig. 1; EX2012 ¶162; *Ariad*, 598 F.3d at 1350 (Fed. Cir. 2010) (“an adequate written description requires a precise definition, such as by structure, ... of species falling within the genus sufficient to distinguish the genus from other materials”). The specification describes and tests 90 examples of the claimed molecules. *See supra* §II.C.2; EX2010 ¶¶72-134. The examples include a diverse range of structures, including: symmetrical and non-symmetrical molecules (EX1001, 158:64-159:3, Fig. 13D; *see also id.*, 18:6-20 (covering knobs-into-holes)); structures with fusion to an Fc (*id.*, 158:54-159:39, Figs. 13, 14); and structures with no Fc region (*id.*, 160:55-67, Fig. 16). EX2012 ¶¶161-233. And these molecules collectively bind seven of the ten Fzd receptors and the LRP5 and LRP6 coreceptors and incorporate a variety of known antigen-binding fragments (*e.g.*, full IgG, Fv, Nab or VHH, Fab, scFv, and F(ab')₂). *See supra* §§II.C.2, IV.A.2; EX2012 ¶¶175-181, 218. The specification additionally discloses binders for all 10 Fzds. EX1001, tbl. 1B. From this, a POSA would understand that the inventors were in possession of the claimed tetravalent molecules across the full range of target receptors, structures, and antigen-binding fragments. EX2012 ¶¶175-181, 189-207, 208-223; EX2010 ¶¶71-73, 155. Thus, the specification provides sufficient description to a POSA of the claimed tetravalent molecules, with a 2:2 Fzd:LRP5/6 stoichiometry, that bind Fzd and LRP5/6 receptors in view of POSA’s knowledge of Fzd and LRP5/6 binding regions and

antibodies and antigen-binding fragments generally. *Falko-Gunter*, 448 F.3d at 1367-68.

Federal Circuit precedent supports this conclusion, including *Ariad* and *Falko-Gunter* (discussed *supra* §IV.A.1), *Teva*, *Ajinomoto*, and *Monsanto*. In its recent *Teva* decision, the Federal Circuit reversed JMOL of invalidity for lack of written description (and enablement) after a jury finding of validity. *Teva*, 172 F.4th at 1371. The Federal Circuit confirmed that, in the case of a “well-known genus [of antibodies] used as part of a different invention,” the specification, when “read in light of the background knowledge in the art,” can provide a representative number of species even where the specification does not contain examples explicitly covering the full scope of the claim language. *Id.* at 1374-80. The patents there made “clear that their claimed invention is the *use* of anti-CGRP antagonist antibodies, or humanized versions thereof, *to treat headache*—not such antibodies themselves.” *Id.* at 1376. The Federal Circuit concluded “[a] reasonable jury could have found that anti-CGRP antagonist antibodies *themselves* and methods of making them were well known, replete, or extensively described in the prior art.” *Id.* at 1376. “Although the specification disclosed just one humanized anti-CGRP antagonist antibody,” a POSA “would have understood from the specification that all humanized anti-CGRP antagonist antibodies treat headache.” *Id.* at 1376-77.

Several other Federal Circuit cases discussed in *Teva* “are particularly

instructive for analyzing written description ... *where the claim pertains to a well-known genus that is not, itself, the invention.*” *Id.* at 1374. In *Ajinomoto*, the Federal Circuit rejected a written description challenge to a claim reciting a bacterium comprising the yddG gene together with a “genus of ‘more potent promoter[s],”” where the patent specification disclosed only four examples of such promoters and cited to a prior-art article disclosing them. *Ajinomoto Co. v. Int’l Trade Comm’n*, 932 F.3d 1342, 1358-59 (Fed. Cir. 2019). The Federal Circuit held that the claim’s recitation of “more potent promoters” did not render written description inadequate because the patent specification “ma[de] clear that its invention was ‘identifying the yddG gene encoding a membrane protein’”—*not* a genus of “more potent promoters”—and the “genus of more potent promoters was already well explored in the relevant art by the time of the ... patent’s invention.” *Id.* at 1359. The court also stated that “the representative-species inquiry is directed to whether the inventor ‘has truly invented the genus’ as opposed to ‘a research plan, leaving it to others to explore the unknown contours of the claimed genus.’” *Id.*

In *Monsanto*, the Federal Circuit determined “it was unnecessary” for the patent at issue “to include specific gene sequences when referring to the CaMV 35S promoter,” recited in the claims, “to meet the written description requirement” because POSAs “knew the DNA sequences of several strains of the CaMV virus, the location of the CaMV promoters, and the DNA sequences of several CaMV 35S

promoters.” *Monsanto Co. v. Scruggs*, 459 F.3d 1328, 1337 (Fed. Cir. 2006) (granting summary judgment of no invalidity).

The same result is appropriate here, where the claims and specification indicate that the invention is the claimed molecules that have a 2:2 Fzd:LRP5/6 stoichiometry and bind to Fzd and LRP5/6 receptors, not Fzd and LRP5/6 binding regions generally. The specification also describes antibodies and antigen-binding fragments that bind Fzd and LRP5/6 receptors, each of which were individually known in the prior art and described in the specification, as well as tetravalent formats, which likewise are described throughout the specification. A POSA would have understood from the specification that the inventors were in possession of the claimed tetravalent molecules that incorporate the known genus of Fzd and LRP5/6 binding regions in a novel way. *See* EX2012 ¶162.

4. Petitioner’s Arguments Fail

First, Petitioner argues that the examples disclosed in the specification are not sufficient to describe the full claim scope because the total number of claimed molecules is “at least 130 million,” and the specification evaluated “just 29 ... possible tetravalent formats.” Pet. 38-40. This fails for the reasons discussed above, and because the law does not require an applicant “to describe in the specification every conceivable and possible future embodiment of his invention.” *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (quoting *Rexnord*

Corp. v. Laitram Corp., 274 F.3d 1336, 1344 (Fed. Cir. 2001)) (cleaned up); *Falko-Gunter*, 448 F.3d at 1366 (a “specification do[es] not [have to] contain examples explicitly covering the full scope of the claim language”) (quoting *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005)).

In any event, Petitioner’s estimate is unreliable because it requires testing every possible combination of binding regions despite the body of research already known about the desired targets. EX2012 ¶¶210-211. Further, Petitioner grossly overestimates the number of target combinations at “over **35,000** different Fzd/L[RP] combinations.” Pet. 30. Petitioner’s declarant reaches this number by counting cross-reactive binding sequences as their own “target” (e.g., counting Fzd1, Fzd2, **and** Fzd1/Fzd2 as three individual targets for a single binding region). EX1003 ¶¶113-23; EX2010 ¶171. This is incorrect because each binding region will bind only one target receptor, regardless of cross-reactivity with multiple targets. EX2010 ¶¶170-171. Correctly calculated, there are at most **400** possible Fzd-LRP5/6 binding target combinations for a molecule with a 2:2 Fzd:LRP5/6 stoichiometry (10 Fzds at Fzd binding region 1 * 10 Fzds at Fzd binding region 2 * LRP5 or LRP6 at LRP5/6 binding region 1 * LRP5 or LRP6 at LRP5/6 binding region 2 = 400 target combinations). EX2010 ¶170.

Second, Petitioner mischaracterizes the tested molecules as all being “bispecific (i.e., each Fzd and each LRP binding region binds to the same site,

respectively), while claim 1 encompasses trispecific and tetraspecific molecules binding multiple different sites in Fzd and/or LRP5/6.” Pet. 44-45. Petitioner’s argument demands more than the law requires, for “a specification need not show an actual reduction to practice in order to satisfy the written-description requirement.” *Teva*, 172 F.4th at 1377.

Even still, the ’278 Patent discloses hundreds of binding sequences targeting all ten Fzd receptors, LRP5, and LRP6 (*see, e.g.*, EX1001, tbls. 1B, 2A), which it teaches may be used in combination with “standard techniques well known to those of skill in the art” to prepare molecules containing binding regions for “one *or more* Fzd receptors and one *or both* of LRP5 and/or LRP6.” *Id.*, 16:37–39; EX2012 ¶162. The specification also teaches that binding regions may be cross-reactive with multiple Fzds or with both LRP5 and LRP6. *Id.*, 121:44-46 (LRP5/6 binding regions may bind to “one or both of LRP5/6”), Table 1B (disclosing multiple cross-reactive Fzd binding regions); EX2012 ¶¶109, 215. That is more than sufficient to convey possession of trispecific and tetraspecific embodiments—*e.g.*, molecules in which the two Fzd binding regions target two different Fzd receptors, one LRP5/6 binding region targets LRP5, and the other targets LRP6. EX2012 ¶109.

The Patent also provides numerous working examples of multispecific molecules. For example, the majority of Fzd binding regions tested in the Examples are cross-reactive with multiple Fzds (*see* EX1001, tbls. 1B, 3; EX2020 at 10:10-13;

Pet. 33), such that the tested molecules are bispecific (binding two of the same Fzd receptors and two of the same LRP5/6 receptors) **and** trispecific (binding two different types of Fzd receptors and two of the same LRP5/6 receptors). EX2012 ¶109; EX1001, tbls. 1B, 3; *see* EX2010 ¶91. From these examples, a POSA would understand the specification to disclose that other tri- and tetraspecific molecules would also work because of cross-reactivity. EX2012 ¶¶109, 215.

Third, Petitioner incorrectly cites Tao (EX1072) for diabody “formats that were unknown to a POSA in December 2017 and are materially different from those evaluated in the specification.” Pet. 58. As Dr. Ravetch explains, diabodies were known antibody-derived structures by 2017, and could be made “using standard molecular biology techniques.” EX2012 ¶¶69, 278; EX1001, 14:33-38; *id.* 13:56-64. Moreover, the ’278 Patent expressly says that the claimed molecules can be “formatted as a diabody.” EX1001, 21:39-51, 151:23-28, Fig. 1D. Thus, a POSA would have understood the ’278 Patent inventors to be in possession of tetravalent molecules incorporating diabodies, as in Tao. EX2012 ¶278.

Even if molecules in Tao’s format were considered after-arising technology not covered by the Patent, as Petitioner suggests (*compare* EX1002 ¶¶200-203 (arguing, “in Tao’s formats, each of the two Lrp5/6 binding regions is directly linked via a linker moiety to **both** Fzd binding regions”), *with* Pet. 19 (arguing claim 1 requires the LRP5/6 binding regions be “connected directly via a linker moiety to

one and only one Fzd binding region (original emphasis))), this would not be fatal to written description and enablement, which are assessed at the time of the invention. Failure to describe after-arising technology “does not affect the validity of the patent” where it is “not what is claimed” because written description “asks whether that which is claimed is adequately described.” *In re Entresto*, 125 F.4th 1090, 1098 (Fed. Cir. 2025).

Fourth, none of Petitioner’s cited cases “presented the circumstances of ... this case—i.e., a well-known genus used as part of a different invention.” *Teva*, 172 F.4th at 1379. And none of the patent disclosures in Petitioner’s cited cases are comparable to the extensive disclosures of the Patent here. In *Juno* (Pet. 55), the patent did not “disclose representative species” of the genus where the specification disclosed only *one* scFv that could function as a “binding element” for CD19 and “only four or five CD19 scFv species were known at the time.” *Juno Therapeutics, Inc. v. Kite Pharma Inc.*, 10 F.4th 1330, 1333-34, 1341, 1342 (Fed. Cir. 2021). In *AbbVie* (Pet. 57), the patent claimed a genus of “structurally diverse antibodies,” but the 300 antibodies disclosed were “all derived from Joe-9” (a single antibody) and shared “90% or more sequence similarity in the variable regions,” with 200 of those antibodies—all generated by varying *one* amino acid in a Joe-9 mutation—sharing “99.5% sequence similarity in the variable regions.” *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1291, 1300 (Fed. Cir. 2014). And

the problem in *Idenix* was that a POSA was “deprived of any meaningful guidance into what compounds beyond the examples and formulas, if any, would” effectively treat HCV. *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019). The patent owner there conceded as much, explaining that “not all 2' methyl up ribonucleosides will be effective to treat HCV.” *Id.* at 1159. That is not the case here, where a POSA would understand from the specification and the examples that the claimed tetravalent molecules activate Wnt signaling, as confirmed by 90 different tested molecules, coupled with the fact that the Patent describes both Fzd and LRP5/6 binders as “known in the art.” EX1001 at 79:63-66, 116:25-29. Tetravalency is thus a precise structural definition that is “sufficient to distinguish [the claims] from other materials.” *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1363 (Fed. Cir. 2011).

B. Claim 1 Is Not Invalid for Lack of Written Description Even Under Petitioner’s Claim Construction

The written description analysis under Patent Owner’s construction in Section IV.A also applies under Petitioner’s construction, which additionally requires a “molecule that is biologically active” or a “Wnt agonist.” Those additional requirements do not change the conclusion that the claims are adequately described.

Based on the specification’s disclosure of a representative number of species, a POSA would understand how to “visualize or recognize” the tetravalent molecules that activate Wnt signaling such that a POSA would understand that the inventors

“invented a genus.” *Ariad*, 598 F.3d at 1350. Petitioner’s assertion that a POSA would need to “empirically evaluate each potential tetravalent format ... hoping that the resulting molecules would ... activate a Wnt signaling pathway,” Pet. 37, is unsupported by its arguments and particularly challenging to credit given that every tetravalent molecule with a 2:2 Fzd:LRP5/6 stoichiometry tested in the examples activated Wnt signaling. EX2012 ¶106; EX2010 ¶¶72-74. Far from merely providing a “wish list of properties,” or a “research” plan (Pet. 34, 37), the specification exhaustively teaches the features sufficient to design a tetravalent molecule, provides detailed descriptions of the components falling within the scope of the claims, and discloses a representative number of embodiments. EX2012 ¶¶162-233. Together, these disclosures inform the POSA the inventors were in possession of the full scope of claim 1. *Id.* ¶162.

The specification describes tetravalent molecules that bind Fzd and LRP5/6 to activate Wnt signaling. EX2012 ¶¶162-272; EX2010 ¶¶70-134. Given this, and the fact that the processes involved in canonical Wnt signaling were well-understood by 2017 (EX2010 ¶¶26-31, 40), a POSA would have understood that the inventors were in possession of tetravalent molecules binding Fzd and LRP5/6 with a 2:2 stoichiometry that “could lead to a surrogate molecule capable of agonizing Wnt activity” (Pet. 3). *See* EX2012 ¶¶234-272; EX2010 ¶¶70-74.

The specification repeatedly discloses tetravalent molecules that are “biologically active” or “Wnt agonists.” For example:

- The invention “provides Wnt pathway agonists.” EX1001, abstract; *see id.*, 1:34-37 (“The present invention relates generally to Wnt signaling pathway agonist molecules ... useful, for example, in modulating Wnt signaling pathways.”), 4:66-5:3.
- “Wnt surrogate molecules of the present invention are biologically active in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the Wnt surrogate molecule is a Wnt agonist.” *Id.*, 16:51-56.
- “The term ‘Wnt agonist activity’ refers to the ability of an agonist to mimic the effect or activity of a Wnt protein binding to a frizzled protein and/or LRP5 or LRP6.” *Id.*, 16:56-58; *see also id.*, 16:58-17:10.

The specification also describes numerous tetravalent molecules that are “biologically active” or “Wnt agonists,” listing 80 illustrative tetravalent molecules in Table 3 and providing examples that demonstrate activation of Wnt signaling in SuperTOPFlash assays by 90 highly varied tetravalent molecules. *See supra* §II.C.2; EX2012 ¶¶255-272; EX2010 ¶¶72-134.

Each example in the specification provides a POSA with detailed evidence that the claimed configuration of 2:2 LRP5/6 and Fzd binding regions agonizes Wnt

signaling. *See* EX1001, 155:14-161:33. Examples 2-18 of the specification tested 90 different tetravalent Wnt surrogate molecules in STF reporter assays and found that ***every tetravalent Wnt surrogate tested was capable of activating Wnt signaling activity***, despite variation in orientation, antigen-binding fragments, binding sequences, and Fzd-LRP5/6 binding targets. *See supra* §§II.C.2, IV.A.3; EX2010 ¶¶72-134; EX2012 ¶106. Changes to the tetravalent molecules impacted potency, but not activation, of Wnt signaling:

- Examples 5-8 and 17 demonstrate that various Fzd-LRP5/6 binder pairings can activate Wnt signaling. EX1001, 156:38-157:29, 161:5-17, Figs. 5-8, 17; EX2010 ¶¶87-100, 128-131; EX2012 ¶¶109, 260, 263.
- Example 9 used an IgG-Nab format, rotating the Nab's attachment point around the IgG, and every orientation tested "activated Wnt signaling to various levels." *Id.*, 157:35-50, Fig. 9; EX2010 ¶¶101-105; EX2012 ¶107.
- Example 13 tested seven tetravalent molecules, including asymmetrical structures, which varied the structure, spacing, and orientation of the binders and all activated Wnt signaling. *Id.*, 158:54-159:3, Fig. 13D-13F; EX2010 ¶¶111-117; EX2012 ¶172.
- Example 14 tested fifteen tetravalent molecules with varied structures, spacing, binding sequences, and binder orientations and "all of these

scFv formats activated Wnt signaling.” *Id.*, 159:36, Figs. 14A-14D; EX2010 ¶¶118-122; EX2012 ¶107.

- Example 15 tested thirteen tetravalent molecules, varying whether the Fzd or LRP binder was in IgG format and the method of HC-LC pairing, all of which “activated Wnt signaling.” *Id.*, 159:54-160:49, Fig. 15; EX2010 ¶¶123-125; EX2012 ¶¶173-183.

That is more than adequate written description. EX2012 ¶¶162, 233.

Further, the specification confirms that a POSA would have known how to identify a “biologically active” “Wnt agonist” molecule at the time of the invention. The specification explains “[m]ethods of measuring Wnt/[β]-catenin signaling are known in the art.” EX1001 at 17:8-10, 117:39-118:36 (describing “[v]arious methods [] known in the art for measuring the level of canonical” Wnt signaling). Those methods include TOPFlash reporter assays, which were widely used and accepted as an accurate and reliable method of identifying canonical Wnt signaling activity in 2017. *Id.*, 118:37-52, 155:14-161:33; EX2010 ¶¶56-58, 62.

Petitioner’s arguments fail. **First**, Petitioner argues that the 29 tested formats identified by Dr. McDonnell are not representative of other claimed formats with respect to Wnt signaling because a given Fzd-LRP5/6 binder pair may produce a response in one format but “fail[] to do so” in another. Pet. 40-43; *id.*, 48-54. This fails because it relies on mischaracterizations of the ’278 Patent’s examples and Dr.

Li's later-dated patent application (EX1081).

According to Petitioner (Pet. 41-42, 50-51), Example 9 shows two claimed tetravalent molecules with no activity. This is incorrect. The 18R5-26 CL and R2M3-26 CL molecules induced a “measurable increase” in Wnt signaling activity:

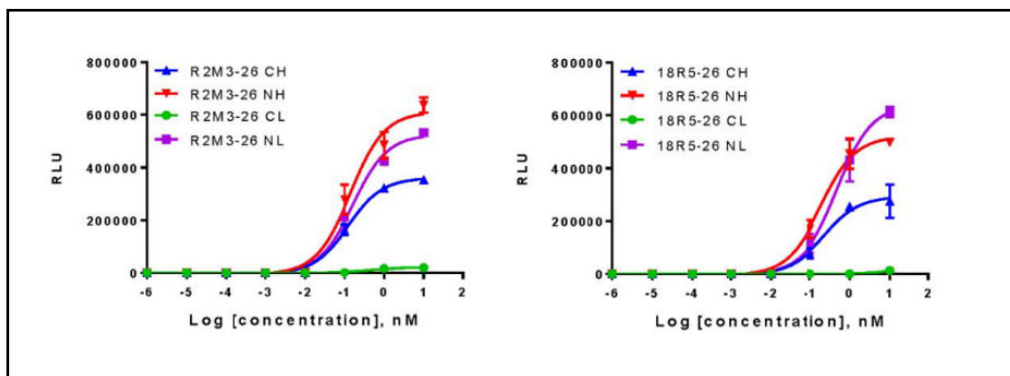


Figure 5: '278 Patent Figs. 9A (left) and 9C (right) (EX1005 at 46)²

EX1001, Fig. 9, 157:44-47; EX2010 ¶¶101-105; EX2012 ¶198; *see also* EX1001, 16:63-17:2 (“Wnt agonists disclosed herein activate, enhance, or increase” canonical Wnt signaling, wherein “‘enhances’ refers to a measurable increase in the level of Wnt/[β]-catenin signaling compared with the level in the absence of a Wnt agonist”).

Petitioner also argues that numerous claimed tetravalent molecules showed no

² Patent Owner includes here and in subsequent figures the color versions found in Provisional Patent Application No. 62/607,875, to which the '278 Patent claims priority. *See* EX1005 at 46.

activity in the absence of R-spondin, suggesting the molecules therefore are not actually “biologically active.” Pet. 48-49. That is misleading. R-spondin is a potentiator: it does not activate Wnt signaling on its own. Rather, the molecule is what activates Wnt signaling, as confirmed by an assay like TOPFlash. *Supra* §II.A.2; EX2010 ¶¶46, 117, 146. And regardless, the description of the examples confirms each of the molecules tested “activated Wnt signaling to various levels.” EX1001, 156:38-45 (Example 5, including R2M3-25 and -27), 156:60-67 (similar; Example 6, including 18R5-28), 157:27-29 (similar; Example 8, including 1R-G05-26), 158:54-63 (similar; Example 13, including 26:Fc:17SB9); EX2010 ¶¶92-93, 100, 117; EX2012 ¶¶263, 172, 183.

Petitioner then argues that Figure 11A of Dr. Li’s later-dated patent application (EX1081) shows that tetravalent molecules combining 18R5 (Fzd binder) and 1115.3 (LRP6 binder) became inactive when the binder orientation was inverted. Pet. 42-43, 53. However, the data does not show inactivity; instead, it shows a difference in degree of activity. *See* EX2012 ¶¶199, 201. Figures 10E and 10F depict the same data shown in Figure 11A at a more granular scale and show the molecules activate canonical Wnt signaling (EX1081 at 13 (lines 16-24), Figs. 10E, 10F, 11A; EX2012 ¶201:

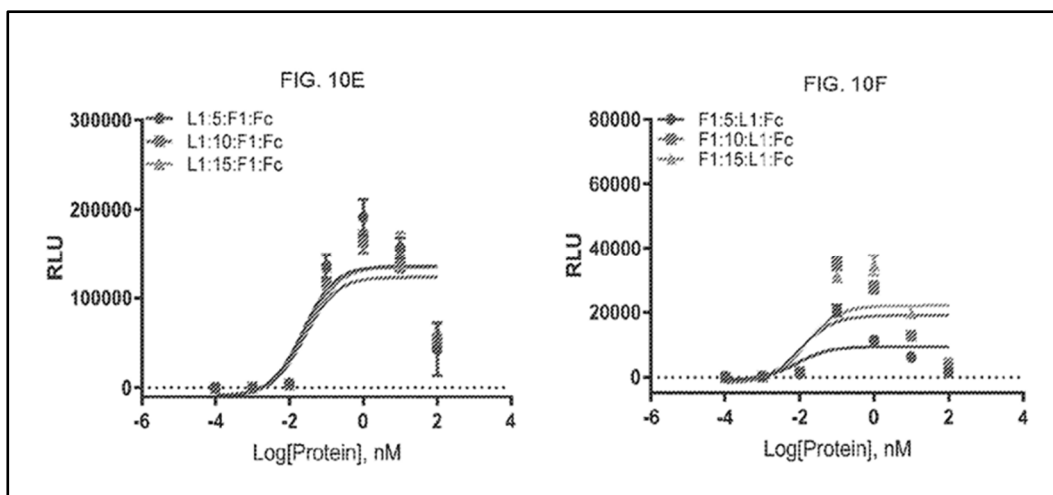


Figure 6: EX1081 Figs. 10E and 10F

Second, contrary to Petitioner’s claim that “the chance of activating Wnt signaling for any given pairing of Fzd and LRP5/6 binding region sequences unpredictably varies format-to-format,” Pet. 41, a POSA would understand from the specification that the inventors understood that molecule format—and concentration (Pet. 52 (discussing so-called “hook effect”)); EX2012 ¶¶267, 269; EX2010 ¶¶150-151—affected signaling potency, **not** the claimed tetravalent molecules’ ability to activate Wnt signaling. *See supra* §II.C.2.

Third, Petitioner argues that the 90 tetravalent molecules disclosed are not representative because a POSA cannot “extrapolate from one molecule to another with different Fzd specificity” and not every target combination was tested. Pet. 46. This fails. Petitioner’s sole cited example for this point is Figure 5A from Dr. Li’s later-dated application. Pet. 46-47 (citing EX1081). That figure demonstrates that the tetravalent molecule (blue, below) **did** result in Wnt signaling, or biological

activity, particularly given the scale on the y-axis:

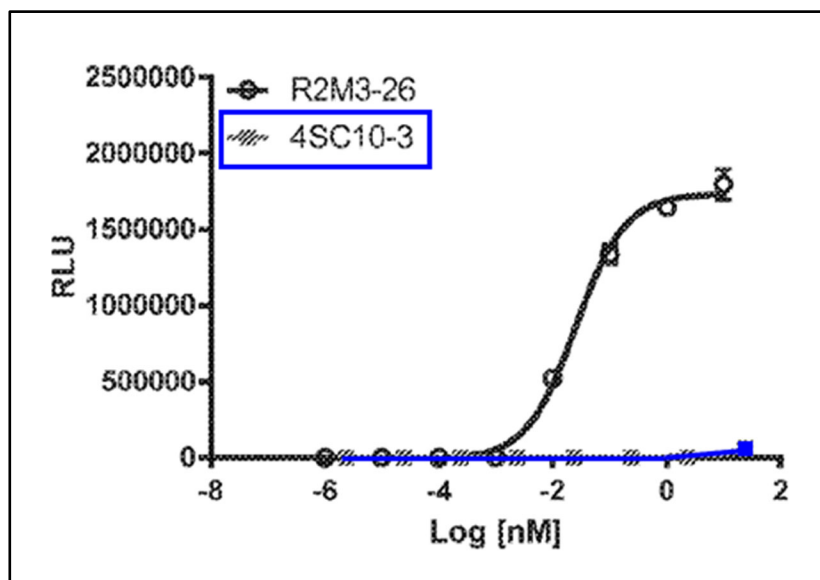


Figure 7: EX1081 Figure 5A (annotated)

EX1081 at 209; *compare id.*, Fig. 5A (0 to 2,500,000 RLU), *with id.*, Fig. 10E-10F (0 to 300,000 and 80,000 RLU, respectively); EX2012 ¶222. And the application includes methods of treating particular diseases (*e.g.*, EX1081, cl. 50); whether the Wnt molecule is *effective* at signaling such that it can treat a disease differs from the base question of whether the molecule activates Wnt signaling at all. EX2012 ¶222.

Fourth, Petitioner argues that because of unpredictability in the art, finding a tetravalent molecule that modulates the Wnt pathway would have required trial and error in 2017. Pet. §V.A.2. This ignores the claims (which require Fzd and LRP5/6 binders in a tetravalent format) and the specification (which discloses molecules in that format that activated Wnt signaling). Petitioner then identifies three alleged sources of “unpredictability”: (1) “components and stoichiometries,” (2) “structures

and expression profiles,” and (3) “other variables.” Pet. 32-37. None compels invalidity for lack of written description: the “proper inquiry is whether the patentee has provided an adequate description that ‘in a definite way identifies the claimed invention’ in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing.” *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015) (quoting *Ariad*, 598 F.3d at 1352).

Components and stoichiometries (Pet. 32). The alleged unpredictability in the Wnt signaling interactions of natural Wnt and non-Wnt ligands cannot be attributed to the claimed tetravalent molecules, which are narrowly tailored to bind to specific Fzd and LRP5/6 targets and implicate only the canonical pathway. EX2010 ¶¶31-46. Claim 1 recites molecules with a 2:2 Fzd:LRP5/6 stoichiometry, and the specification teaches that those molecules activate Wnt signaling. *See supra* §II.A.1. Nevertheless, Petitioner asserts that a lack of “consensus as to the ‘stoichiometry of the putative Wnt-FZD-LRP6 (or LRP5) complex’” renders the claimed molecules unpredictable in activating Wnt signaling. Pet. 32. Not so. The Patent’s examples consistently demonstrate that the claimed molecules with a 2:2 Fzd:LRP5/6 stoichiometry will activate Wnt signaling. EX2010 ¶¶45, 72-74; EX2012 ¶¶106, 303.

Not limiting the claims to particular Fzd/LRP target combinations that activate Wnt signaling does not render them unpredictable. Pet. 32-33. A POSA

would understand from the specification's extensive disclosures that the inventors were in possession of tetravalent molecules with binding sequences targeting Fzd and LRP5/6 receptors with a 2:2 Fzd:LRP5/6 stoichiometry that will function as Wnt agonists, *i.e.*, provide a measurable increase in Wnt signaling activity. EX2010 ¶¶72-134; EX2012 ¶¶224-232; EX1001, 16:63-17:2. And to the extent testing is desired to confirm activation, a POSA would not indiscriminately make and test every embodiment—they would approach the task with specific molecular design goals. EX2012 ¶¶163, 289, 317. The claims here are unlike the invalid claims in *PureCircle*, where only one species was disclosed and the POSA would have blindly tested at least 9,000 candidate enzymes in the hopes of identifying “potential active candidates.” *PureCircle USA Inc. v. SweeGen, Inc.*, No. 2022-1946, 2024 WL 20567, at *3 (Fed. Cir. Jan. 2, 2024). Here, a POSA can reliably predict and confirm, without “extensive trial and error” testing, that the claimed tetravalent molecules will function as Wnt agonists.

Further, the fact that the claims do not specify the stoichiometry of the Fzd and LRP5/6 target receptors *at a more granular level* does not create a lack of predictability. Pet. 33. In every example, the '278 Patent demonstrated that tetravalent molecules with a 2:2 Fzd:LRP5/6 stoichiometry will activate Wnt signaling, regardless of which specific target combinations of two Fzd and two LRP5/6 receptors would be optimal for a particular application. EX2010 ¶¶72-74,

156; EX2012 ¶¶238, 303. Petitioner provides no examples of tetravalent molecules where multiple LRP5/6 binding regions bound to the same LRP5/6 receptor, let alone that this might stop Wnt signaling. EX2010 ¶157; EX2012 ¶243.

In characterizing the state of the art, Petitioner cites to publications from 2002 to 2012, before the '278 Patent's 2017 priority date. *See* Pet. 32 (citing EX1033; EX1053; EX1082). But a POSA's understanding of the Wnt signaling complex evolved substantially in the years preceding the priority date, leading to substantial growth in the field and the first Wnt Signaling Gordon Research Conference in 2017. *See* EX2010 ¶¶26-31.

Structures and expression profiles (Pet. 34). That Wnt surrogate molecules target different tissues that “express[] different amounts and types of Fzd and Lrp5/6 receptors” over time does not detract from the inventors' possession of the claimed invention. *See* EX2012 ¶247. As explained earlier in this Section (IV.B), a POSA would understand that Examples 9 and 13-15 modify the orientation and spacing of the tested molecules' binding regions and still activate Wnt signaling in every instance, regardless of the level of activity. *See* EX2010 ¶¶101-105, 111-125, 158; EX2012 ¶¶171-172, 296. Consistent with this, the Patent teaches that “spacing between the binding domains can be used to *modulate* the signal strength” and can be selected “depending on the *desired use* of the Wnt surrogate molecule.” EX1001, 116:48-52.

Other Variables (Pet. 35). That different natural “Wnt and non-Wnt ligands interact with their corresponding receptors with different strengths and at different sites” does not render the claims invalid. Even if a different molecule could provide more potent activation by binding with a greater affinity or specificity, or binding a different epitope, the claims (even under Petitioner’s construction) require only that the tetravalent molecule *activate* Wnt signaling and not a specific degree of activation. EX2010 ¶¶137-138; EX2012 ¶222; *see infra* §VI.A. Each of the 90 tetravalent molecules tested in the ’278 Patent activated Wnt signaling. EX2010 ¶¶72-74. Further, it was understood in 2017 that activation of Wnt signaling primarily results from bringing Fzd receptors and LRP5/6 coreceptors into interaction by heterodimerizing them, regardless of which epitope is bound on each receptor. EX2010 ¶44.

C. Claims 2-5 Have Adequate Written Description

Dependent claim 4, directed to pharmaceutical compositions of the Wnt surrogate molecules of claim 1, has adequate written description for the reasons discussed above as to claim 1 and the specification’s disclosures. EX1001, 133:1-136:38; EX2012 ¶284. Dependent claims 2-3 and 5 recite the further structural limitation that the Fzd binding region is a full IgG and the LRP5/6 binding region is a VHH (claim 2), and further specify the attachment locations of the LRP5/6 binding regions (claims 3 and 5, depending on claim 2). A POSA would understand the

inventors were in possession of these inventions for the reasons discussed above for claim 1 and also because the claimed tetravalent formats are described and tested in the specification. *Compare, e.g.*, EX1001, 155:14-156:14, 157:15-50, 161:1-17, *with* EX1001 cls. 2-3, 5; *see also* EX2012 ¶¶280-283.

V. CLAIMS 1-5 ARE ENABLED

Enablement requires that a patent teach POSAs how to make and use the full scope of the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). “The key word is ‘undue’, **not** ‘experimentation,’” and enablement is not precluded by the necessity for some experimentation such as routine screening. *Id.* at 737. Moreover, “the specification must enable the full scope of the invention as defined by its claims.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023). In other words, the enablement inquiry is measured against the claims as written. *Id.*; *CFMT, Inc. v. Yieldup Int’l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003) (patent did not need to enable a specific level of contaminant removal where none was recited in claims).

A specification does not have to “describe with particularity how to make and use every single embodiment within a claimed class”; rather “it may suffice to give an example (or a few examples) if the specification also discloses ‘some general quality ... running through’ the class that gives it ‘a peculiar fitness for the particular purpose.’” *Amgen*, 598 U.S. at 610-11.

The specification provides extensive guidance to a POSA seeking to make and use the claimed tetravalent molecules, including 90 working examples, hundreds of binding sequences, the tetravalent structure, and detailed descriptions of how the tetravalent molecules and their familiar constituent parts can be generated and evaluated. *Supra* §§II.C, IV.A.1-3, IV.B; EX2021 at 96-97; EX2022 at 93-95; *see also* EX2012 ¶¶44-88, 291. Petitioner’s enablement analysis rehashes its failed written description arguments, relying on mischaracterization of the Examples and exaggeration of the complexity of Wnt signaling that ignores the scope and guidance provided in the specification. With that specification, a POSA can practice the full scope of the claims without undue experimentation. *In re Wands*, 858 F.2d at 737.

A. Claim 1 Is Enabled

1. The Claim Scope Is Bound by Structure and Commensurate with Its Disclosures

Claim 1 has “meaningful structural limitations” (*contra* Pet. 63), including tetravalence in the form of a 2:2 stoichiometry of Fzd and LRP5/6 binding regions. EX1001, cl. 1. The specification describes a range of tetravalent molecules across the scope of these claims, varied by binding sequences, antibody or antigen-binding fragment types, structure, and orientation. *Supra* §§II.C, IV.A.1-3, IV.B. Thus, claim 1’s scope is not “exceedingly broad,” but rather would allow a POSA to carry out the invention of claim 1 given the extensive disclosure of the genus. *Id.*; EX2012 ¶¶286-290; *see* EX2010 ¶¶72-134 (describing Examples 2-18).

2. The Specification Provides Extensive Guidance and 90 Working Examples Across Claim 1's Scope

The specification presents 90 “working examples” and extensive “direction or guidance” that favors enablement, even under Petitioner’s proposed “biologically active” construction. *In re Wands*, 858 F.2d at 737.

Examples 2-18 test 90 tetravalent molecules embodying the claim, each of which activated Wnt signaling activity. *Supra* §§II.C.2, IV.B. These working examples are not only numerous, but representative across claim 1’s scope. *Supra* §IV; EX2012 ¶¶291-299. The working examples are accompanied by disclosure of bivalent molecules, using the same Fzd and LRP5/6 binders, that were “ineffective” in activating Wnt signaling. EX1001, 157:55-158:47, 159:40-47; EX2010 ¶¶106-110, 120-121. Together, the examples teach that the claimed tetravalent molecules with a 2:2 Fzd:LRP5/6 stoichiometry will activate Wnt signaling, as required by Petitioner’s proposed construction. *Supra* §IV.B; EX2010 ¶¶72-74; EX2012 ¶294.

Beyond the examples, the specification provides guidance regarding the design, generation, and evaluation of the claimed tetravalent molecules, enabling a POSA to identify working embodiments and practice the claims. Tables 1B and 2A disclose sequences for 91 confirmed Fzd binders and 211 CDR sequences, and the specification incorporates descriptions of processes for making and evaluating these molecules. EX1001, tbls. 1B, 2A; EX2021 at 96-97; EX2022 at 93-95; EX2012 ¶¶292-293; EX2010 ¶71. The specification also describes design blueprints for the

claimed tetravalent molecules, *e.g.*, formats incorporating diabodies. *Supra* §§IV.A.2-3; EX1001, 21:39-51, 116:52-62, 151:23-28; EX2012 ¶¶278, 319. With these teachings in hand, a POSA need not “engage in painstaking experimentation” to practice the claim. *Amgen*, 598 U.S. at 614.

Although claim 1, properly construed, does not require the claimed tetravalent molecules to function as Wnt agonists, the specification nevertheless provides clear teaching that the claimed molecules with a 2:2 stoichiometry consistently activate Wnt signaling. *Supra* §§II.C.2, IV.B. Petitioner’s suggestion that the specification does not disclose “how other untested formats, target combinations, and binding region sequences would function as a Wnt surrogate” or “how to identify appropriate ... valency” (Pet. 64) are irreconcilable with this teaching. *See* EX2012 ¶¶295-298; *see also* EX2010 ¶156. Petitioner’s demands for the *ideal* geometry, attachment locations, flexibility, and specificity (Pet. 64-65) are not tied to the claim requirements, even under Petitioner’s construction. *See supra* §IV.B.

3. The State of the Art, Level of Skill, and Predictability in the Art Support Enablement

Petitioner’s next tranche of *Wands* factors also favors Surrozen. **First**, the level of skill in the art relevant to the ’278 Patent is high—both parties agree that a POSA in this space had an advanced Ph.D. degree in the relevant space and years of experience in the relevant fields. *Supra* §II.B; Pet. 10; *see also* EX2012 ¶21. Petitioner makes no mention of this skill level. Pet. 66-67. **Second**, the state of the

art was advanced as of 2017, and the inventors pointed to such past building blocks in their specification. *Supra* §§II, IV.A.1; EX2012 ¶¶44-88, 300-305; EX2010 ¶¶26-31, 40. **Third**, because of the inventors’ work disclosed in the ’278 Patent, the predictability in the art favors Surrozen: Building from the well-developed understanding of Fzd and LRP5/6 binding regions and antibody engineering, the inventors surprisingly discovered that a 2:2 ratio provided “efficient” Wnt signaling. *See* EX1008 at 4170-71 (“greatly superior activity” of 2:2 Wnt surrogates was “surprising and unexpected in view of the prior art and understanding in the field”). Petitioner has not shown otherwise.

Petitioner’s characterization of the field as “nascent and unpredictable” (Pet. 65) relies on irrelevant aspects of the field, such as noncanonical signaling or natural Wnt ligands’ interaction with noncanonical coreceptors, and improperly minimizes the ’278 Patent’s substantial disclosures. EX2010 ¶¶31-48; EX2012 ¶¶300-305; *see supra* §§II.A, II.C, IV.A.1-3, IV.B.

Specifically, Petitioner argues that tetravalent, multispecific molecular formats were “nascent and unpredictable” because there was no universal “one best format” and no tetravalent therapy has been FDA-approved. Pet. 65-66. But this ignores that the claimed tetravalent Wnt surrogates are built on a foundation of well-characterized components, including Fzd and LRP5/6 binders, various antibodies and antigen-binding fragments, and methods of identifying, purifying, and

combining those components. EX2012 ¶¶44-111. While true that the inventors created a novel tetravalent molecule through their claims, paving the way for FDA-approved therapies, this does not render the claims unpredictable or non-enabled. A POSA following the '278 Patent's teachings was able to create the tetravalent molecules claimed in 2017. EX2012 ¶305.

Petitioner's characterization of the Wnt signaling field as nascent and "bewilderingly complex," citing to Dr. Kahn's 2014 article (EX1043) (Pet. 66), is no more availing. Petitioner's analysis is largely premised on factors—like noncanonical signaling, ligand-receptor interactions beyond Fzd and LRP5/6, the behavior of natural Wnt ligands, and the unresolved stoichiometry of the Wnt-Fzd-LRP5/6 complex—that would not come into play or materially impact the practice of the claimed invention. EX2010 ¶¶31-48. The claim scope and disclosures of the '278 Patent excise several of Petitioner's alleged sources of unpredictability (Pet. 66), even under Petitioner's construction: *first*, the claims focus on canonical signaling by claiming Wnt surrogates that "enhance the *canonical Wnt/β-catenin* signaling pathway" by simultaneously binding Fzds and LRP5/6. EX1001, 1:54-59, 117:33-35; *see* EX1008 at 4006 (distinguishing the claimed molecules, which agonize canonical signaling); EX2010 ¶33. *Second*, a POSA would recognize via the disclosure of 90 tetravalent molecules that combining two Fzd and two LRP5/6 binding regions reliably activates such Wnt signaling, providing predictability to the

claimed molecules regardless of factors like “local cellular conditions” and the site- and receptor-specific behavior of *natural* Wnt ligands (Pet. 66). *See* EX2010 ¶¶41-50, 72-74.

Petitioner’s remaining factors specific to Wnt signaling (Pet. 66-67) do nothing to further its arguments, as it has not shown why a POSA, with the ’278 Patent’s disclosures, could not make and use the claimed invention. For instance, the “lack of [a] comprehensive[]” assay for both canonical and noncanonical Wnt signaling and the alleged “cell-type dependency” of canonical assays (Pet. 66) do not prevent a POSA from identifying whether the claimed tetravalent molecules activate Wnt signaling in a TOPFlash assay. EX2010 ¶¶53, 62-65; EX2012 ¶¶315-316. And it is not a sign of non-enablement that a “molecule specifically developed to activate Wnt signaling” was not FDA-approved in 2017 nor today (Pet. 66-67). EX2012 ¶¶87, 301; *see also* EX2010 ¶¶47-48.

Contrary to Petitioner’s argument that a POSA would not have “derived any general rule or set of parameters for making tetravalent, multispecific molecules for activating Wnt signaling,” Pet. 67, the substantial guidance of the ’278 Patent tells a POSA that combining LRP5/6 binding regions with Fzd binding regions in a 2:2 ratio will reliably induce Wnt signaling. *See* EX2012 ¶¶234-272; EX2010 ¶¶72-134; *In re Wands*, 858 F.2d at 737.

4. Practicing the Full Scope of the Claim Does Not Require Undue Experimentation

Even under Petitioner’s Wnt agonist construction, the ’278 Patent teaches that a tetravalent molecule with a 2:2 Fzd:LRP5/6 stoichiometry will activate Wnt signaling even when parameters, such as the binding sequences, orientation, and linker length, are varied. *Supra* §§II.C.2, IV.B. The inventors also provided extensive teachings on the process of purifying and characterizing Fzd and LRP5/6 binders (EX1001, 22:31-34, 80:36-39; EX2021 at 96-97; EX2022 at 93-95) and the orientations, structures, and antibody engineering methods (*e.g.*, knobs-into-holes and charge pairing) by which those binders could be combined (EX1001, 17:55-21:51, 150:26-161:33). *Supra* §§II.C, IV.A.1-3; EX2012 ¶¶44-111. These disclosures allow a POSA to practice the full scope of claim 1 without trial-and-error identification of working embodiments.

While “a considerable amount of experimentation is permissible” when such experimentation is routine and the specification guides its direction, such experimentation is not necessary here. *In re Wands*, 858 F.2d at 737. As in *Teva*, where the court noted the “more relevant ‘research assignment’ in th[at] case would have been determining which humanized anti-CGRP antagonist antibodies *treat headache*,” *Teva*, 172 F.4th at 1381 (original emphasis), here, the relevant “research assignment” was determining which of the Fzd and LRP5/6 binding regions, ***when combined in the tetravalent format claimed***, activate Wnt signaling. Further, as Dr. Ravetch and Dr. Willert explain, in view of the Patent’s teachings and advancement

of the art, activities such as purification, expression, and characterization of a large number of binding regions and tetravalent molecules, would not be undue experimentation in the fields of antibody engineering, Fzd and LRP5/6 receptors, and Wnt signaling. EX2012 ¶¶307-318; EX2010 ¶¶57, 163-166. Given that Fzd and LRP5/6 binding regions (and methods of making them) were known (*supra* § II.C.1; EX2012 ¶¶162, 311), and all of them work in the claimed tetravalent structures, “undertaking to find or make all of them would—in the context of these claims—be more akin to extra credit than a necessary research assignment left to others to complete.” *Teva*, 172 F.4th at 1381.

Assuming, *arguendo*, that Petitioner’s three phases of experimentation—making Fzd and LRP5/6 binders, forming tetravalent molecules, and testing them “for Wnt agonism”—are necessary, Petitioner overstates the burden of experimentation at each step, and further ignores the Patent’s teachings that all tetravalent molecules comprising two Fzd and two LRP5/6 binders induced Wnt agonism (Pet. 67-69). Furthermore, Petitioner’s emphasis on the time it would take to make and test every format (Pet. 70-71) is misplaced: “enablement is not measured against the cumulative time and effort it takes to make every embodiment,” *Amgen*, 598 U.S. at 615.

Identification and characterization of the binding affinities of Fzd and LRP5/6 binding sequences was a familiar process in 2017 and far less “time-consuming and

resource-intensive” than Petitioner suggests (Pet. 67). EX2012 ¶309. The specification discloses, by incorporation, methods for purifying and characterizing the binding affinities of these sequences and provides extensive exemplary binders. *Supra* §II.C.1. A POSA could identify and confirm the binding affinities of additional sequences binding to each of the Fzd and LRP5/6 target receptors without undue experimentation. *Contra* Pet. 68; *see also* EX2012 ¶309.

Designing the claimed tetravalent molecules incorporating these binding regions would not have required undue experimentation in 2017. A POSA with a Ph.D. and 5 years’ experience in antibody engineering would, in 2017, have understood how to express, purify, and assemble the binding regions into tetravalent molecules using antigen-binding fragments and tetravalent structures known in the art and familiar to the POSA. EX2012 ¶307.

Petitioner’s characterization of the third step purportedly required to practice the claims—testing for Wnt agonism, only required if Petitioner’s construction is adopted—exaggerates the experimentation required both because it assumes a POSA would need to make and test each molecule to confirm agonism and overstates the experimentation involved in doing so. **First**, a POSA reading the ’278 Patent would understand—without testing each molecule—that the inventors were in possession of tetravalent molecules with a 2:2 Fzd:LRP5/6 stoichiometry, which reliably activate Wnt signaling. *Supra* §II.C.2, IV.B; *see* EX2010 ¶¶72-74. **Second**,

the specification guides a POSA to evaluate signaling activity using a TOPFlash assay, a familiar and reliable method that does not take thousands of years to perform. *Supra* §§II.A.2, IV.B; EX2010 ¶¶57, 162-166; *contra* Pet. 70-71.

While Petitioner attempts to overcomplicate the art in characterizing TOPFlash assays, Petitioner's discussions of Wnt5a, R-spondin, cell types, and concentration-dependent signaling levels are not examples of "inconsistent responses," Pet. 70, but predictable consequences of well-understood phenomena that a POSA can interpret and account for in the context of the claimed tetravalent molecules (*e.g.*, by using a β -catenin-dependent assay at multiple concentrations, with R-spondin). EX2012 ¶316; *see* EX2010 ¶¶62-65, 135-151, 161. The Federal Circuit has explained that where claims did "not require a particular level of stability or a particular magnitude of increase" in stability and "[a]djusting variables may be relevant to optimizing the stability of a given" composition, this alone was not enough to render the claims not enabled, particularly where the defendant "proffered no evidence that any experimentation, let alone undue experimentation, with those variables would be necessary in order to practice the claimed invention." *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014). So too here; Petitioner merely recites variables, none of which have been shown to render the claims "inoperable." *Id.* Given the Patent's guidance, determining whether assay results reflect Wnt signaling is straightforward.

5. Supreme Court and Federal Circuit Precedent Support Enablement and Not Petitioner's Arguments

First, claim 1 is directed to the 2:2 Fzd:LRP5/6 stoichiometry that permits simultaneous binding of those regions. Like the method of treatment claim in *Teva*, claim 1 is valid. There, the Court found *Teva* claims to methods of treating headaches using humanized anti-CGRP antagonist antibodies to be “unlike the claims in *Amgen* and *Baxalta*” that claim antibodies defined solely by function, because the claims were not to the antibodies “*themselves*”; instead, they claim only the use of such antibodies” in treating headache. *Teva*, 172 F.4th at 1381. So too here, where the claims are focused on the overarching design of the molecule reciting a 2:2 tetravalent format, rather than the binding regions *themselves*. As in *Teva*, where the court concluded that a POSA’s “assignment was completed” by the inventors and the claims are enabled because “*all* such antibodies work for that purpose,” *id.*, here, even under Petitioner’s Wnt agonist construction, the Patent teaches that *all* such combinations of Fzd and LRP5/6 binding regions into the format claimed will work to activate Wnt signaling and the claims are also enabled.

Second, *Amgen* and *Baxalta* are inapposite. The claims here do not claim every antibody that binds to Fzd or LRP5/6 receptors, but rather the limited combination of such binding regions in a tetravalent format with a 2:2 Fzd:LRP5/6 stoichiometry.

Claim 1 is also supported by extensive disclosures far exceeding *Amgen*’s 26

“narrow” amino acid sequences and *Baxalta*’s 11 antibodies, all of which were monospecific and monoclonal. *Amgen*, 598 U.S. at 602-04; *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1364 (Fed. Cir. 2023). The ’278 Patent discloses a broad range of Fzd and LRP5/6 binding regions and tetravalent structures. *Supra* §§II.C, IV.A.1-3. Even without these substantial disclosures, the tetravalence and stoichiometry of the claimed molecules confer a “peculiar fitness” for activating canonical Wnt signaling, such that “an example (or a few examples)” suffice for enablement. *See Amgen*, 598 U.S. at 610-611 (quotation omitted).

Third, *Seagen* is inapposite, as the specification lacked the ’278 Patent’s extensive teachings and assurances. *Seagen Inc. v. Daiichi Sankyo Co.*, 160 F.4th 1322, 1325-27 (Fed. Cir. 2025). There, the court noted that “[w]hether and how” the claims’ functional requirement that the “drug moiety is intracellularly cleaved in a patient” was met unpredictably depended on the components of the linker protein, meaning a POSA would need to perform assays to determine *whether* such cleavage occurred for “any given [antibody-drug conjugates] with a given drug moiety.” *Id.* at 1325, 1333. In contrast, the ’278 Patent teaches that every molecule with the claimed tetravalence and 2:2 stoichiometry activates Wnt signaling, including through extensive and diverse examples. *Supra* §§II.C.2, IV.B; EX2010 ¶¶72-134; EX2012 ¶¶161-233.

Fourth, unlike the *Idenix* claims covering “billions” of compounds requiring

individual testing, the '278 Patent's guidance and working examples avoid the need for "an iterative, trial-and-error process" to identify operative embodiments that activate Wnt signaling. *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1157–59, 1161 (Fed. Cir. 2019). As in *Teva*, and unlike *Idenix*, a POSA would understand from the specification that the inventors here were in possession of Fzd and LRP5/6 binders which can be used in tetravalent Wnt surrogates, and a wide variety of tetravalent molecules that reliably activate Wnt signaling, "thereby obviating any extensive screening to determine which ones [work]." *Teva*, 172 F.4th at 1381.

B. Claims 2-5 Are Enabled

Claims 2-5 of the '278 Patent are enabled for the reasons discussed in connection with claim 1. Claims 2, 3, and 5 are additionally enabled because the '278 Patent explicitly discloses the tetravalent structures they claim. *See supra* §IV.C.

VI. CLAIMS 1–5 ARE NOT INDEFINITE

A. "Wnt Surrogate Molecule" Is Not Indefinite

The Board need not reach this ground of invalidity if it construes "Wnt surrogate molecule" as Surrozen has proposed. *Supra* §III.A. Even if the Board reaches this ground, Petitioner's indefiniteness arguments flowing from its flawed claim constructions fail. *Supra* § III.A.3.

Petitioner construes “Wnt surrogate molecule” to be “biologically active,” and argues that this renders the claims indefinite because there is allegedly “conflicting ... guidance on how to determine whether a candidate molecule is ‘biologically active.’” Pet. 75. But claims “should be construed to preserve their validity.” *Phillips*, 415 F.3d at 1327. And Petitioner is wrong that the claims (1) require the Wnt surrogate molecule be “biologically active ... in activation of Wnt signaling,” and (2) broadly cover both the canonical and non-canonical Wnt signaling pathway.

First, the inventors did not act as a lexicographer to require the claimed Wnt surrogate molecules to be “biologically active.” *Supra* § III.A.3. Second, the specification confirms that Wnt surrogate molecules that bind to both Fzd and LRP5/6 are directed to the canonical pathway, not the noncanonical pathway. EX1001, 1:51–59 (“Canonical Wnt signals also involve [LRP5/6] as co-receptors ... in addition to Fzds.”); *see* EX2010 ¶¶27, 33. The specification also confirms that the inventors were focused on canonical Wnt signaling: “the Wnt surrogate molecules of the invention enhance the *canonical* Wnt/ β -catenin signaling pathway,” *id.*, 117:33-38; *see also* EX1008 at 4006—rendering Petitioner’s complaints about “multiple conflicting assays for canonical or noncanonical Wnt signaling” irrelevant. Pet. 76 (capitalization normalized); *supra* §II.A.1-2; EX2010 ¶¶32, 53; EX2012 ¶330. Petitioner’s quotation of other parts of the specification describing noncanonical Wnt signaling ignores that the claims, which “define the invention,”

Phillips, 415 F.3d at 1312, recite molecules that bind to both Fzd and LRP5/6.

Petitioner also argues that the claims are indefinite because they cover Wnt surrogate molecules that (i) activate both canonical and non-canonical Wnt signaling pathway in (ii) any number of different cells, which (iii) can be confirmed by any number of assays disclosed in the Patent. Pet. 76-77; Pet. 81-82. Even assuming Petitioner is correct (which Surrozen disputes), that is not a definiteness problem. A “claim is not indefinite just because it is broad.” *Niazi Licensing Corp. v. St Jude Med. S.C., Inc.*, 30 F.4th 1339, 1347 (Fed. Cir. 2022) (collecting cases). Rather, the claims need only “inform, with reasonable certainty, those skilled in the art about the scope of the invention” to be definite under §112(b). *Nautilus Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

Even if the Board agrees with Petitioner’s flawed claim construction, the claims are not indefinite. Foremost, Petitioner cannot complain of indefiniteness when its own construction defines what it means to be “biologically active”: a Wnt surrogate molecule is biologically active if it “bind[s] to one or more Fzd receptor and to one or more of LRP5 and LRP6,” and if it “activat[es] Wnt signaling.” Pet. 17. This definition comes from column 16 of the ’278 Patent, which explains how to determine whether a Wnt surrogate molecule is a “Wnt agonist.” It says: “the Wnt agonists disclosed herein activate, enhance, or increase the canonical Wnt/[β]-catenin signaling pathway.” EX1001, 16:63-17:2; *see also* EX2012 ¶324. It then

defines “enhances” as “a measurable increase in the level of Wnt/[β]-catenin signaling compared with the level *in the absence of a Wnt agonist*, e.g., a Wnt surrogate molecule disclosed herein.” EX1001, 16:63-17:2; *see also* EX2010 ¶137; EX2012 ¶324. And the ’278 Patent provides guidance on how to measure such an increase in the level of Wnt/[β]-catenin signaling. EX2010 ¶¶56, 162; EX2012 ¶¶325-327.

As the Petition admits, “the specification lists at least five different assays” for measuring canonical signaling. Pet. 77 (quoting EX1001, 117:39-44). The specification explains any of these assays may work to measure an increase in Wnt/[β]-catenin signaling, but it repeatedly directs skilled artisans to the TOPFlash assay (*e.g.*, EX1001, 118:37-51; EX2010 ¶162), which skilled artisans would recognize as the “go-to assay for evaluating canonical Wnt signaling in cells.” EX2010 ¶56; *see also* EX2012 ¶328. The inventors also used SuperTOPFlash assays to measure an increase in the level of Wnt/[β]-catenin signaling for numerous different Wnt surrogate molecules. EX1001, 155:14-161:33 (using Wnt-dependent “STF” assays); EX2010 ¶55 (“STF” refers to “SuperTOPFlash”); *see also* EX2012 ¶335.

Petitioner does not provide a single example where “the same candidate molecule” exhibited “opposite responses, depending on the assay” used. *Contra* Pet. 76; *see also* EX2012 ¶¶331-332; EX2010 ¶¶135-151. “[T]he mere possibility of

different results from different measurement techniques” is insufficient to render a claim indefinite, where there is “no evidence ... that different measurement techniques in fact produced significantly different results for the same sample.” *Takeda Pharm. Co. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359, 1366–67 (Fed. Cir. 2014).

Dow Chemical Co. v. Nova Chemicals Corp. (Canada), 803 F.3d 620, 634–35 (Fed. Cir. 2015) (Pet. 78) is inapposite. In *Dow*, “[n]either the patent claims nor the specification [] discusse[d] the four methods” for measuring the maximum slope or “provide[d] any guidance as to which method should be used.” *Id.* at 634; *see also* *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1344–45 (Fed. Cir. 2015) (holding claims indefinite where patentee provided conflicting statements in prosecution history and specification did not mention the terms). But here, the Patent discusses each of the assays—all “known in the art for measuring the level of canonical Wnt/ β -catenin signaling,” EX1001, 117:39–40—and encourages skilled artisans to use the SuperTOPFlash assay through its repeated use in the examples. *See id.* at 155:14–161:33, Figs. 2–18; EX2010 ¶162. Unlike in *Dow*, where there was no testimony that a skilled artisan “would choose [the patentee’s selected] method over the three known methods,” expert testimony here confirms that the TOPFlash assay was highly regarded and widely used in the field and would have been the “go-to assay” for measuring Wnt/ β -catenin signaling in 2017. EX2010 ¶56.

Petitioner next argues the design of the inventors' TOPFlash assay examples is flawed, including because of (1) "the lack of threshold and positive controls," and (2) the use of R-spondin. Pet. 78-81. These are red herrings.

First, Petitioner's "lack of threshold and positive controls" argument begins from the faulty premise that a POSA would not know if a given molecule is a Wnt agonist without comparing its activity to that of a natural Wnt protein. Pet. 79. The Patent is clear, however, that the comparator is a "measurable increase" compared to "the level *in the absence of a Wnt agonist*." EX1001, 16:63-17:2; EX2012; EX2010 ¶137. The Patent then tells skilled artisans how they can use well-known Wnt-specific assays to determine whether a given molecule activates Wnt signaling, *i.e.*, by comparing its activity to *the absence of* a Wnt agonist. EX2012 ¶¶324, 333, 335; *see also* EX2010 ¶¶137-142. Nothing more is required. *See* EX2012 ¶335.

U.S. Well Services, LLC v. Stewart is inapposite because the specification there provided no objective boundary for what constituted a "high pressure" as compared to, *e.g.*, "medium pressure." 2025 WL 798863, at *2 (Fed. Cir. Mar. 13, 2025). Here, the '278 Patent provides a yardstick by which to measure whether a Wnt surrogate molecule is a "Wnt agonist"—it tells skilled artisans to look for "a measurable increase in the level of Wnt/[β]-catenin signaling *compared with the level in the absence of a Wnt agonist*." EX1001, 16:63-17:2; *see also* EX2012 ¶324. Those are clear, objective boundaries, and §112(b)'s definiteness requirement

requires nothing more. *See Barrette Outdoor Living, Inc. v. Fortress Iron, LP*, 156 F.4th 1353, 1367 (Fed. Cir. 2025) (“[A]n inventor ‘need not define his invention with mathematical precision in order to comply with the definiteness requirement.’”).

The inventors also chose a method for measuring such an increase, *i.e.*, the TOPFlash assay, which is Wnt-dependent, meaning any reporter activity reflects activation of the canonical pathway. EX2010 ¶¶58, 162. Thus, if a Wnt surrogate molecule demonstrates **any** level of Wnt signaling activity in a TOPFlash assay, it is necessarily a Wnt agonist. The inventors specifically implemented such **negative controls** in their examples, *i.e.*, by measuring Wnt signaling activity for Wnt surrogate molecules compared to, *e.g.*, molecules that comprised only the Fzd binding region (and thus are not Wnt agonists). EX2010 ¶¶60, 142; EX2012 ¶336. These examples reinforce that there are objective boundaries by which to measure the scope of the claims.

In Example 5, for example, the inventors measured the activity levels for ten different Wnt surrogate molecules and three non-agonist molecules (R2M3-24, R2M3-34, and R2M3 IgG which consist of Fzd binders, but no LRP5/6 binders). *See* EX1001, 156:32–52, Figs. 5A–F; EX2010 ¶87. As the inventors affirmed, R2M3-28 and the other five Wnt surrogate molecules “**activated Wnt signaling to various levels.**” EX1001, 156:43-45; EX2010 ¶87; EX2012 ¶¶258-262, 338. The non-Wnt

surrogate molecules, by contrast, “displayed no activity.” EX1001, 156:45-52; *see also id.*, 156:64–67, Fig. 6D (similar results in Example 6). Indeed, in every example, the non-Wnt agonist did not induce reporter activity, whereas the Wnt surrogate molecule did. EX2012 ¶336; *see also, e.g.*, EX1001, 155:14-40, Fig. 2D (reporting assay results for RM23-26, which “consists of a Fzd binder (R2M3) and a LRP6 binder (26)” and “induced reporter activity,” and R2M3 IgG, which did not have an “LRP binding arm” and “did not induce reporter activity”), 155:47-156:14, 156:38-67, Figs. 3D, 5A, 5C–5G, 6A, 6C, 6D; EX2010 ¶¶90, 104, 142.

Second, Petitioner’s R-spondin argument (Pet. 80) incorrectly assumes that one must compare the activity of the claimed molecules to that of a natural Wnt protein to know whether it’s a Wnt agonist. This is incorrect as discussed above. EX2010 ¶¶137-138. And it is also misleading as to the role R-spondin plays in an assay designed to measure activation of Wnt signaling. R-spondin is a potentiator for signaling, meaning it amplifies or boosts already-existing activity (*e.g.*, the height of an already-existent signal); it does not **activate** Wnt signaling on its own. EX2010 ¶¶117, 146; EX1001, 155:29-36 (explaining that R-spondin “enhance[s]” reporter activity). For example, as shown below (*infra* Fig. 8), Example 5 tested various Wnt surrogate molecules both in the presence of R-spondin, and without R-spondin. The R2M3 IgG molecule (which, again, is not a Wnt agonist because it binds to Fzd only (*see* EX1001, 159:29–36)) showed no reporter activity, regardless

of the presence of R-spondin, whereas the Wnt surrogate molecules showed increased activity with R-spondin. EX1001, Figs. 5A, 5E; EX2010 ¶¶87, 145; EX2012 ¶336. Thus, although certain Patent examples show lower activity without R-spondin compared to when R-spondin is present, that does not make it “confusi[ng] as to whether or not these molecules are ‘Wnt surrogate molecules.’” Pet. 81; EX2010 ¶¶117, 146; *see also* EX2012 ¶338. They are, and testing them in the presence of R-spondin only confirms as much.

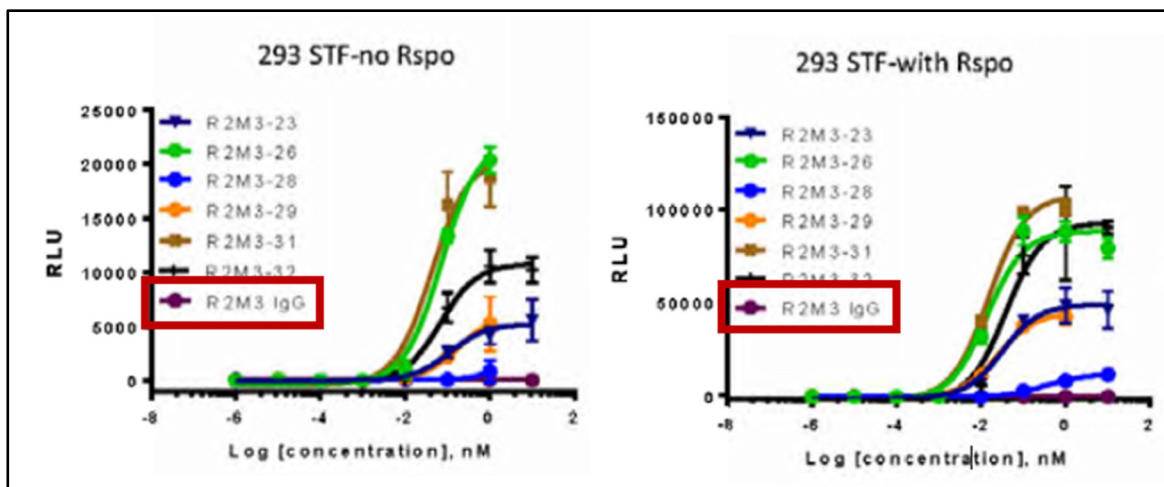


Figure 8: '278 Patent Figures 5A (left) and 5E (right) (EX1005 at 42)

Petitioner next argues indefiniteness because a given Wnt surrogate molecule may activate Wnt signaling in some cell lines, but not others. Pet. 81-82 (discussing 18R5-28); Pet. 76-77 (citing Pet. 6 (“the Wnt5a ligand was found to both inhibit and induce the activation of canonical Wnt signaling in TOPFlash assays depending on

the cell type tested” (emphasis omitted))).³ The law is otherwise. In *Nevro Corp. v. Boston Scientific Corp.*, the Federal Circuit rejected the patent challenger’s argument that claims to a device configured to generate a “paresthesia-free” signal were indefinite, notwithstanding that “a given signal will eliminate paresthesia in some patients, but not others.” 955 F.3d 35, 40 (Fed. Cir. 2020). Even if Petitioner is correct that a given molecule may or may not activate Wnt signaling, depending on the cell line, as in *Nevro*, that “does not render the claims indefinite.” *Id.*

Moreover, Petitioner’s argument is carefully worded to be intentionally misleading. Ignoring Example 6’s express statement that the molecules tested therein “demonstrated ability to activate Wnt signaling,” EX1001, 156:64–67, Petitioner cites to one of the tested molecules, “18R5-28,” and argues that “*in the absence of R-spondin*,” this molecule “failed to activate Wnt signaling in 293 cells but activated Wnt signaling in A375 cells.” Pet. 82. What Petitioner omits, however, is that *in the presence of R-spondin*, 18R5-28 activated Wnt signaling in every cell type tested. See EX1001, Figs. 6C (BNL.CL2 cells), 6D (293 cells); see also *id.* Fig.

³ The Wnt5a molecule is a natural ligand which inhibits canonical Wnt signaling “through the activation of [the Ror2] receptor,” but activates canonical Wnt signaling during “Fzd 4 and LRP5 coreceptor expression.” EX1056 at 2, 11. The claimed Wnt surrogate molecules are designed to do the latter, not the former.

6B (showing activation for A375 cells even without R-spondin); EX2010 ¶¶93, 149. Thus, if a POSA had any question as to whether a specific molecule activated Wnt signaling, it could confirm as much by testing it in the presence of R-spondin to amplify its signal. *See* EX2010 ¶¶63, 149; *contra* Pet. 82.

Petitioner concludes by arguing the claims are indefinite because some molecules “lost their agonistic effects at higher concentrations.” Pet. 83. But Petitioner’s own cited case law confirms that they are not. In *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-84 (Fed. Cir. 2003) (Pet. 77), the Federal Circuit held that the claim “synergistically effective amount” “encompass[ed] any dosage amount that can achieve therapeutic synergy.” In doing so, the Court rejected GSK’s argument that “a formulation falls outside the scope of the claims if a given antibiotic, bacteria, and disease combination provides no synergy,” because *that* “reading of the claim is indefinite.” *Id.* at 1384.

Petitioner advances a similar argument here that the claims are indefinite because a skilled artisan would not know if a given molecule is a Wnt agonist because its agonist activity may change depending on, *e.g.*, the molecule’s concentration, or cell line in which it is tested. Pet. 81-83. But even under Petitioner’s construction, the claims require nothing more than the claimed tetravalent molecule be a Wnt agonist—and “once a particular [molecule]” activates Wnt signaling “under any circumstance,” it is a Wnt agonist. *Geneva*, 349 F.3d at

1384; *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1254-55 (Fed. Cir. 2008) (“*Because the patent claims at issue [in Geneva] did not identify the specific bacteria*, we rejected the proposed construction because ‘a given embodiment would simultaneously infringe and not infringe the claims, depending on the particular bacteria chosen for analysis.’”).

Halliburton does not compel a different conclusion. *Halliburton* concerned a term of degree, “fragile gel,” which is decidedly different than “Wnt surrogate molecule,” which is not a term of degree. 514 F.3d at 1256. In holding the claims indefinite, the Federal Circuit explained that they were “ambiguous as to the requisite degree of the fragileness of the gel, the ability of the gel to suspend drill cuttings (i.e., gel strength), and/or some combination of the two,” and there was no “upper bound of fragileness” contemplated. 514 F.3d at 1256. Moreover, as the Court in *Nevro* later explained, the indefiniteness problem with which *Halliburton* was concerned was “not [that] infringement could only be determined after use, but [that] infringement *could not be determined at any time*.” 955 F.3d at 40. That problem is nonexistent here: A skilled artisan could readily determine whether a Wnt surrogate molecule activates Wnt signaling (a binary “yes” or “no” question) through use of standard, widely-accepted STF reporter assays. EX2010 ¶¶56-58, 61; EX2012 ¶342. Even under Petitioner’s construction, the claims are not indefinite.

**B. Rejecting Petitioner’s Proposed Construction of the “Linker”
Limitation Does Not Render the Claims Nonsensical or Indefinite**

Petitioner argues that if the Board does not adopt Petitioner’s construction of the “linker” limitation (which the Board should not for the reasons discussed (*supra* §III.B)), then the claims would be nonsensical and indefinite.⁴ This, too, is wrong.

As with its first indefiniteness argument (*supra* §VI.A), Petitioner conflates purported claim breadth with the requirements for definiteness. Pet. 84 (arguing “a broader construction ... would further render all claims nonsensical and indefinite”). There is also nothing “nonsensical” about giving these claims their plain-and-ordinary meaning—and Petitioner’s cited case (Pet. 84) does not suggest otherwise. *Horizon Pharma, Inc. v. Dr. Reddy’s Lab ’ys Inc.*, 839 F. App’x 500, 505 (Fed. Cir. 2021) (“Reading the claim literally, a dose form, which is an inanimate object, cannot set a goal.”); *id.* (citing *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1366-67 (Fed. Cir. 2016) (holding claims describing the extraction of machine code instructions from something that did not have machine code instructions indefinite as “nonsensical in the way a claim to extracting orange juice from apples would be”)).

Petitioner’s “nonsensical” argument focuses entirely on its view that the

⁴ Patent Owner’s responses apply with equal force to claim 5, which Petitioner mentions briefly at the end of its indefiniteness argument. Pet. 87; *see also* EX2012 ¶346.

claims require “direct” connection. Pet. 85-87. Referring to Figure 1A, Petitioner first argues that allowing “indirect” connection would render “the specification’s characterization of various formations that fall within the claim scope ... meaningless.” Pet. 85. Petitioner specifically focuses on the use of the word “fused” in connection with Figure 1A and argues that, if “‘fused’ encompasses indirect connection[s],” then the Nab in Figure 1A would be “‘fused’ to the C-termini of both the heavy and light chains” of the IgG simultaneously. Pet. 85. This is yet another red herring.

The claims require only that “each of the two LRP5/6 **binding regions** is fused to one of the two Fzd **binding regions** via a linker moiety.” EX1001, cl.1. In Petitioner’s annotated Figure 1A (Pet. 85), the red “Nab” is one such binder or binding region, and the black antibody is an IgG antibody that is the other binder or binding region. *See also* EX1001, 150:32-37, 155:17-29 (Example 2, testing the R2M3 Fzd binder “in the form of an IgG”), cl. 1 (the binding regions may be “an antibody or antigen-binding fragment of the antibody”); EX2012 ¶¶345-346. In both figures, the “Nab” is fused to the IgG “via a linker moiety”—regardless of where on the IgG said linkage occurs. *See id.* The linkage *in that example* happens to be a “direct linkage” (as Surrozen understands Petitioner’s convoluted construction), but as explained above, the Patent provides examples where there is an “indirect” connection via a linker moiety because of, *e.g.*, an intervening Fc region between

the binding regions. *Supra* §III.B, Figure 2; *see* EX2012 ¶140. There is nothing nonsensical about this. *See* EX2012 ¶¶151, 345.

Petitioner’s complaint (Pet. 85) that a skilled artisan would not know in this figure where the binding region on the IgG starts and ends makes no sense considering the Patent itself states, the molecules in that figure comprise “one or more Fab or antigen-binding fragment thereof and one or more VHH or sdAb or antigen-binding fragment thereof,” and that further, “the Fab is present in a full IgG format.” EX1001, 18:48–52, 62; EX2012 ¶347. Petitioner’s citation to *Infinity Computer Products v. Oki Data Americas, Inc.*, 987 F.3d 1053, 1062 (Fed. Cir. 2021), is thus irrelevant, but it is also inapposite. The problem in *Infinity* was that patentee introduced a term during prosecution to distinguish it from the prior art (“passive link”) and then used that term inconsistently throughout prosecution in a way that made it impossible for the public to determine where the unclaimed “passive link” ends and where the claimed “computer” begins. *Id.*, 1059-60. Unlike in *Infinity*, here, there are no “flat contradiction[s]” that deprive the public of notice of “what is still open to them.” *Id.*, 1060 (quoting *Nautilus*, 572 U.S. at 909).

Petitioner next assumes the conclusion that “one of the two Fzd binding regions” means “one and only one of the two Fzd binding regions.” Pet. 86-87. As explained above, the plain and ordinary meaning is not so restricted. *Supra* §III.B.

Finally, Petitioner argues that any construction other than the one it proposes

would “make the challenged dependent claims incomprehensible.” Pet. 86. That, too, is wrong. Focusing first on claim 3, that claim defines *where* on the Fzd binding region to which the LRP5/6 binding region is linked. By way of dependency, the Fzd binding regions are a full IgG, and the LRP5/6 binding regions are a VHH. EX1001, cl.2. Claim 3 specifies that the LRP5/6 binding region (*i.e.*, the VHH) is “fused” to a specific location on the Fzd binding region, *e.g.*, the N-terminus of the IgG’s heavy chain. By the very nature of being a dependent claim, claim 3’s use of the term “fused” is narrower than claim 1’s use of the term “fused” because it claims a specific connection location between binding regions, whereas claim 1 merely requires the binding regions be fused “via a linker moiety.” *See* EX2012 ¶346.

VII. CLAIMS 1 AND 4 ARE NOT ANTICIPATED BY GARCIA

“Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention *arranged as in the claim.*” *Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008) (quotation omitted) (original emphasis). Here, Garcia fails to disclose all claimed elements because it does not teach a “tetravalent, multispecific Wnt surrogate molecule” that has *two* Fzd binding regions and *two* LRP5/6 binding regions. Garcia therefore does not anticipate claims 1 and 4.

During prosecution, the Examiner reviewed and issued an obviousness objection over Garcia US (EX1011), which Petitioner acknowledges is

“substantively identical” to the Garcia reference now asserted by Petitioner (EX1004). EX1008 at 2973–75, 3982–84; Pet. 15 n.2. The Examiners concluded, *on their own*, that “Garcia [US] does not teach dual variable domain (DVD) format of bispecific antibody” (*i.e.*, one of the claimed tetravalent formats) and relied on secondary reference Wu in their obviousness rejection. *Id.* Dr. Li subsequently confirmed the Examiners’ understanding that Garcia US did not disclose tetravalent bispecific molecules—it “only describe[s] Wnt surrogate molecules having 1:1 Fzd binder:Lrp5/6 binder stoichiometry”—and explained that Garcia US “did not suggest or provide any motivation for a person skilled in the art to design a tetravalent molecule as claimed.” EX1008 at 4168.

Petitioner makes two arguments as to why the Examiners misunderstood Garcia’s teachings, but neither have merit. *First*, Petitioner argues that Garcia’s vague reference to a “dimer” in paragraph 56 means that Garcia teaches “a tetravalent molecule having two binding regions for Fzd and two binding regions for Lrp5/6.” Pet. 88. Not so. As Dr. Ravetch explains, paragraph 56 serves to define what Garcia’s Wnt surrogate molecule can be: a polypeptide with “*a* binding domain for Fzd [] joined to *a* binding domain for Lrp5/6.” EX1004 at 12, [0056]; EX2012 ¶357. As the Petition acknowledges and as Dr. Li explained in his declaration, that is plainly a disclosure of a polypeptide with a 1:1 stoichiometry of Fzd:LRP5/6. Pet. 88; EX1008 at 4168, ¶4.

To get to two Fzd and two LRP5/6 binding domains in a single molecule, Petitioner conflates two distinct biochemical properties: a molecule’s valency and the number of polypeptide chains in its structure. Petitioner’s quoted sentence from Garcia says its molecules may consist of a single polypeptide chain, or two or more such chains (*i.e.*, a dimer or higher-order multimer), but says nothing about their valency—the number of ***binding domains*** the molecule contains. *See* EX2012 ¶356. For example, as Garcia explains, “[i]ntact antibody ***tetramers*** are comprised of two heavy chain-light chain ***dimers***.” EX1004 at [0096]. Yet, “[w]hen natural antibodies fold ..., the heavy and light chains are brought together in three-dimensional space so that they create a ***single*** hypervariable antigen binding site.” *Id.* In other words, Garcia itself describes a ***dimer*** structure that is ***monovalent***, dispelling any notion that its mention of dimers and multimers in connection with its description of a bivalent Wnt surrogate molecule in paragraph 56 somehow discloses a ***tetravalent*** molecular structure with ***four*** binding domains. *See* EX2012 ¶356. Petitioner also cannot use Garcia’s post-priority application (EX1014), filed in 2018 after the inventors’ provisional application (EX1005) was filed in 2017, to import non-existent disclosure into Garcia’s earlier application. Pet. 16.

Second, Petitioner argues that Dr. Li somehow “confirms that the ‘dimer’ described in Garcia includes two Fzd binding regions specifically binding to two Fzd receptors,” *see* Pet. 90—but his declaration refutes that. He unequivocally states

that “Garcia et al. **only** described Wnt surrogate molecules having 1:1 Fzd binder:Lrp5/6 binder stoichiometry, and did not suggest or provide any motivation for a person skilled in the art to design a tetravalent molecule as claimed.” EX1008 at 4168; *see also* EX2012 ¶358. Dr. Li’s declaration confirms Petitioner’s interpretation of Garcia is incorrect.

Petitioner nonetheless hyper-focuses on Dr. Li’s reference to aggregation of a molecule he synthesized in the “1:1 configuration ... described by Garcia” (Dr. Li calls it contamination (EX1008 at 4170-71, ¶6)), arguing that this purported aggregation is a “newly-discovered property” inherent to Garcia. Pet. 89 (citing *Abbott Lab’ys v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1368 (Fed. Cir. 2006)). Petitioner, however, fails to show the contamination Dr. Li refers to is a “property” of Garcia’s molecules at all, let alone a “newly-discovered” one that is “**necessarily present**, or inherent” in Garcia. *Abbott Lab’ys*, 471 F.3d at 1368 (quoting *Schering*, 339 F.3d at 1377). *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995) is instructive. *Glaxo* affirmed a finding of no inherent anticipation where it was undisputed that practicing an example in the prior-art patent “could yield [polymorph] crystals of either” (unclaimed) Form 1 or (claimed) Form 2 of ranitidine hydrochloride. *Id.* at 1047. That was legally insufficient, so the district court “correctly rejected the [inherent] anticipation defense.” *Id.* at 1047-48. So too here. Petitioner has put forward no evidence that Garcia’s Wnt surrogate polypeptides will

necessarily aggregate, or that if they do, they will necessarily have four binding regions comprised of two Fzd and two LRP5/6 binding regions.

Finally, even assuming Petitioner's read of Garcia is correct (it is not), Petitioner still fails to show Garcia anticipates because nowhere does the Petition explain whether and how Garcia discloses each of the claims' limitations as Petitioner construes them.

First, Petitioner makes no attempt to show the "tetravalent dimeric Wnt surrogate molecule" purportedly disclosed in Garcia (EX1002 ¶262) is "biologically active" in agonizing Wnt signaling, as its own flawed interpretation of the preamble term "Wnt surrogate molecule" requires. *See* Pet. 17. Instead, Petitioner appears to uncritically accept as true Garcia's statement that it discloses "Wnt signaling agonist molecules." *See* Pet. 88 (quoting EX1004 at [0009], [0056]). That approach contradicts Petitioner's own purported criticisms of the '278 Patent's disclosures. For example, while the '278 Patent's examples repeatedly state that their tested tetravalent molecules "activated Wnt signaling to various levels," Petitioner looks past those express statements in its flawed written description arguments to instead allege those molecules "failed" to do so. *Compare, e.g.*, EX1001, 156:45 (explaining that the molecules tested in Example 5 "activated Wnt signaling to various levels"), *with* Pet. 49 (alleging, with reference to two molecules tested in Example 5, that "multiple molecules still did **not** produce responses in a TOPFlash assay even in the

presence of R-spondin” (original emphasis)). And while Petitioner faults the ’278 Patent’s examples for demonstrating varying levels of signaling activity in different cell lines (Pet. 81-82), using TOPFlash assays to measure signaling activity (Pet. 69-70), and showing that some molecules produced purportedly “minuscule” responses in those assays (Pet. 49), Petitioner ignores that Garcia’s two “working” examples present all of these supposed flaws. EX1004 at Figs. 4, 8A–B, 15; EX2012 ¶354.

Indeed, with respect to enablement, Petitioner argues incorrectly that “the problem here is that it is impossible to predict *which* format, *which* target combination, and *which* binding sequence will have the requisite biological activity.” Pet. 73 (original emphasis). But with respect to anticipation, Petitioner seemingly divines from Garcia (which does not provide a single working example of a tetravalent molecule) a supposed “tetravalent dimeric Wnt surrogate molecule” that possesses such activity. *See* Pet. 88-89; EX1002 ¶262; EX2012 ¶355. Petitioner cannot have it both ways.

Second, Petitioner provides no explanation how each of the LRP5/6 binding regions in Garcia’s alleged “tetravalent dimeric Wnt surrogate molecule” is “connected directly to one and only one” Fzd binding region, as is required under Petitioner’s construction. EX2012 ¶363.

For at least these reasons, Petitioner has failed to show that Garcia anticipates claims 1 and 4.

VIII. CONCLUSION

Petitioner has failed to meet the “more likely than not” standard that any of the challenged claims of the ’278 Patent are unpatentable under any ground raised in its Petition. Surrozen respectfully requests that the USPTO deny institution of Post Grant Review of claims 1–5 of the ’278 Patent.

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this Patent Owner's Preliminary Response complies with the page count limitation outlined in 37 C.F.R. § 42.24. This Patent Owner's Preliminary Response contains a total of 18,558 words and 86 pages, as calculated by Microsoft Word's word-count feature. This total excludes the cover page, signature block, and the parts of the Patent Owner's Preliminary Response exempted by 37 C.F.R. § 42.24(a)(1).

Date: May 26, 2026

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing Patent Owner's Preliminary Response, together with all exhibits and other documents filed therewith, was served by email on the Petitioner's counsel of record at the United States Patent & Trademark Office having the following addresses:

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